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Health and Environmental Effects Profile for Hexachlorocyclohexanes

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16. ABSTRACT

The Health and Environmental Effects Profile for Hexachlorocyclohexanes was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. Hexachlorocyclohexanes has been evaluated as a carcinogen. The human carcinogen potency factors (q_1*) for α-HCH, β-HCH, γ-HCH and T-HCH are 6.34, 1.84, 1.33 and 1.76, respectively, for oral exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ values for α-HCH, β-HCH, γ-HCH and T-HCH are 1000, 1000, 100 and 100, respectively. Existing data are insufficient to determine an RQ value for δ-HCH and ε-HCH.

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ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste and Emergency Response by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA), as well as to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched." The literature search material is current through November, 1985.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include Reference doses (RfDs) for chronic exposures. An RfD is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, RfDs are not estimated in this document series. Instead, a carcinogenic potency factor of q_1* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

Reportable quantities (RQs) based on both chronic toxicity and carcinogenicity are derived. The RQ is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified under CERCLA. These two RQs (chronic toxicity and carcinogenicity) represent two of six scores developed (the remaining four reflect ignitability, reactivity, aquatic toxicity and acute mammalian toxicity).

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA and CERCLA dockets.

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EXECUTIVE SUMMARY

The isomers of hexachlorocyclohexane (HCH) are white or yellowish powders or flakes, with differing odors depending on the isomer. The isomers are soluble to varying degrees in a variety of organic solvents including ethyl alcohol, chloroform, acetone, dioxane, ether and others (Colson, 1979). HCHs can be decomposed by alkaline substances and are expected to undergo reactions typical of alkyl halides including hydrolysis and dehydrohalogenation (Morrison and Boyd, 1973).

Technical grade HCH (T-HCH), a 65:7:17:4:10 mixture of α, β, γ, ε and other isomers of HCH, respectively, is produced by the photochemically-induced reaction between benzene and chlorine in the presence of a free radical initiator. A variety of physical separation methods are used to purify γ-HCH to 99.9% from T-HCH for use as an insecticide (lindane) (Colson, 1979).

γ-HCH is used as an insecticide on hardwood logs and lumber, a variety of seeds, vegetables and fruits, woody ornamentals including Christmas trees, hardwood forests, livestock and pets (external parasite control) and existing structures (control of woodboring beetles and termites) (Federal Register, 1983). Pertinent data regarding uses of the other isomers in the pure state could not be located in the available literature as cited in the Appendix. The technical product has been used as an insecticide in the past but is no longer used as such (Colson, 1979).

Half-lives of γ-HCH in water at 25°C were reported to be 92, 771 and 648 hours in natural water samples from a eutrophic pond in Texas (pH 9.3), a dystrophic reservoir in Louisiana (pH 7.3) and an oligotrophic rock quarry in Indiana (pH 7.8), respectively (Saleh et al., 1982). Hydrolysis experiments in Milli-Q water at pH values of 5, 7 and 9 yielded half-lives of 936, 4331 and 95 hours, respectively (Saleh et al., 1982). Therefore, hydrolysis at alkaline pH values is expected to be important in the fate of γ-HCH, while hydrolysis at acidic and neutral pH values is not. Pertinent data regarding the hydrolysis of the other isomers of HCH could not be located in the available literature; however, all these isomers contain more equatorial bonds than γ-HCH, and since these bonds are generally more stable than axial bonds, it is expected that the remaining isomers will be more stable to hydrolysis than γ-HCH.

First-order photolysis half-lives for γ-HCH of 169, 1791 and 1540 hours were observed in natural water samples from a eutrophic pond in Texas, a dystrophic reservoir in Louisiana and an oligotrophic rock quarry in Indiana, respectively (Saleh et al., 1982). The relatively short photolysis half-life observed in the Texas sample was attributed to the alkaline pH that, it was concluded, generated hydrolysis products more susceptible to photolysis than γ-HCH (Saleh et al., 1982). After 50 days exposure to sunlight, the concentrations of γ- and α-HCH in purified water dropped from ~9300 to ~7600 μg/mℓ and from 1480 to ~1130 μg/mℓ, respectively (Malaiyandi et al., 1982). Pertinent data regarding the photolysis of the other HCH isomers could not be located in the available literature as cited in the Appendix. Direct photolysis, however, is not expected to be a major fate process for any of the HCH isomers since they do not have conjugated unsaturated systems.

Of the γ-HCH added to unsterilized natural waters in capped bottles, <30% remained after 16 weeks (Sharom et al., 1980). About 25% of the γ-HCH in raw wastewater from Cincinnati was removed during aerobic biodegradation in a wastewater treatment plant (Petrasek et al., 1983). Pertinent data regarding the aqueous biodegradation of the other HCH isomers could not be located in the available literature as cited in the Appendix.

The volatilization half-life of γ-HCH has been estimated to be 115 days (Lyman et al., 1982) and 191 days (Mackay and Leinonen, 1975), assuming a depth of 1 m. Volatilization half-lives of 3.2 and 1.5 days were observed for γ-HCH from still and stirred water 4.5 cm deep (Chiou et al., 1980). The measured volatilization half-life of 3.2 days was used to estimate a half-life of 692 days from water 1 m deep. Since the half-lives of 115 and 191 days are of the same order of magnitude as the half-life estimated from experimental data, the former values are considered to be accurate estimates of the tendency of q-HCH to volatilize. Henry's Law Constant values for the other isomers have been estimated and suggest that volatilization of all HCH isomers occurs at a rate dependent upon the rate of diffusion through the air (Lyman et al., 1982). Volatilization of HCH isomers in water is not expected to be significant in the environment.

A mean K_{oc} for γ-HCH of 1080.9 was obtained from K_{oc} determinations on three soils (Rao and Davidson, 1982). Based on this K_{oc} and a low water solubility of 7.5 ppm (U.S. EPA, 1981), γ-HCH is expected to leach slowly to groundwater. K_{oc} values for the remaining HCH isomers were estimated (Lyman et al., 1982) and, combined with the fairly low water solubilities of the isomers, suggest that they are expected to bind fairly tightly to soil and to leach slowly to groundwater. Fifteen years following the application of technical HCH to a sandy loam soil in Canada, >90% of the applied α-, β-, γ- and δ-HCH remained in the upper 20 cm of soil, indicating minimal leaching had taken place (Stewart and Chisholm, 1971).

BCFs for γ-, α-, β- and δ-HCH in a variety of species ranged from 63-1613 (Matsumura and Benezet, 1973; Ramamoorthy, 1985; Kanazawa, 1983; Schimmel et al., 1977; Metcalf et al., 1973; Yamato et al., 1983; Sugiura et al., 1979). No BCF values were available for ε-HCH, but it is expected to bioaccumulate similarly to δ-HCH, to which it bears a close structural similarity. None of the HCH isomers are expected to bioconcentrate significantly in aquatic organisms.

Based on degradation data, the persistence half-lives for γ-HCH in river, lake and groundwater were estimated to be 3-30, 30-300 and >300 days, respectively (Zoeteman et al., 1980). Pertinent data regarding the persistence of the other isomers could not be located in the available literature as cited in the Appendix.

Anaerobic soil preparations were found to readily degrade γ-HCH (Kohnen et al., 1975; Mathur and Saha, 1975; Lichtenstein et al., 1971; Sethunathan and Yoshida, 1973; Haider, 1979). Degradation of α-HCH by anaerobic soils has also been observed (Castro and Yoshida, 1974; MacRae et al., 1984; Haider, 1979). Doelman et al. (1985) observed greater aerobic than anaerobic degradation of α-HCH in polluted soil. Anaerobic degradation of α-, β- and δ-HCH by several organisms has been observed (Haider, 1979). Pertinent data regarding the biodegradation of ε-HCH could not be located in the available literature as cited in the Appendix.

After 50 hours, 26 and 100% of the surface applied γ-HCH remained on Hatboro silt loam and Norfolk sandy loam, respectively (Glotfelty et al., 1984). The low volatility of the γ-HCH was attributed to the dryness of the sandy loam. From a moist soil surface, the γ-HCH content decreased to 50 and 10% of the amount applied after 6 hours and 6 days, respectively, while 50 hours after the application of γ-HCH to dry soil, 88% of the applied compound remained (Glotfelty et al., 1984). Pertinent data regarding the volatilization of the other HCH isomers could not be located in the available literature as cited in the Appendix. The estimated Henry's Law constants, K_{oc} and measured water solubility values suggest that the isomers will bind fairly tightly to soil and will have little tendency to volatilize from dry soils. Volatilization from moist soils, however, may be significant.

γ-HCH concentrations of 0.01-0.319 ppb have been detected in drinking water from various rural and urban areas (Keith et al., 1976; Sandhu et al., 1978; Bevenue et al., 1972). Based on these figures and assuming an average daily consumption of 2 ℓ of water, an average daily γ-HCH intake of 0.02-0.638 μg was estimated. A γ-HCH concentration of 1.3 ppb was detected in Ottawa, Ontario (Kraybill, 1977). The average daily intake based on this figure is 2.6 μg, but this figure is considered to be nonrepresentative since the monitoring data on which it is based is so high relative to the other values. Surface water and precipitation (rain and snow) samples contained measurable concentrations of γ-HCH (U.S. EPA, 1985a; Oliver and Charlton, 1984; Cole et al., 1984; Saleh et al., 1982; Sandhu et al., 1978; Bevenue et al., 1972; Page, 1981; Strachan and Huneault, 1979; Pankow et al., 1984; Brooksbank, 1983; Strachan, 1985). α-HCH has been detected at 2.7-20.3 and 0.45-9.7 ppt municipal drinking water samples collected during the winter and summer, respectively (Williams et al., 1982) and at 17 μg/ℓ in tap water from Ottawa, Ontario (Kraybill, 1977). An average daily intake of α-HCH of 0.90-40.6 ng was estimated, assuming an average daily consumption of 2 ℓ of water (excluding the Ottawa result). Based on the high α-HCH content of the tap water from Ottawa, an average daily intake of 34 μg was estimated. Because of the relatively high value of α-HCH in the Ottawa sample, this value is thought to be nonrepresentative. Samples of surface water and precipitation (rain and snow) from a variety of locations contained α-HCH (U.S. EPA, 1985a; Kuntz and Warry, 1983; Page, 1981; Cole et al., 1984; Strachan and

Huneault, 1979; Eisenreich et al., 1981; Pankow et al., 1984; Brooksbank, 1983; Strachan, 1985). In the Netherlands, β-HCH was found in ng quantities in a variety of locations (Duinker and Hillebrand, 1979). Samples of surface water in the United States contained a mean β-HCH concentration of 0.1725 μg/ℓ (U.S. EPA, 1985a). Pertinent monitoring data for δ- or ε-HCH could not be located in the available literature as cited in the Appendix.

A wide variety of foodstuffs, including dairy products, meat, vegetables, fruits and seafood, contain one or more HCH isomers (Duggan et al., 1983; Steffey et al., 1984; Podrebarac, 1984; Schmitt et al., 1985; U.S. EPA, 1985a). The average daily intake of γ-HCH was estimated to be 0.27 μg, based on the γ-HCH content in foods from 1971-1976, and that of α-HCH was estimated to be 10.5 and 9.1 ng/kg bw/day, based on 1977 and 1978 data, respectively. Since monitoring data in foods are available only for mixtures of the isomers, β-, δ- and ε-HCH, it is not possible to estimate the average daily intakes of individual isomers.

The mean concentration of γ-HCH in positive samples of ambient air in the United States in 1970-1972 was 0.9 ng/m³ (Kutz et al., 1976). Based on this value and assuming an average intake of 20 m³ air/day, the average daily intake of γ-HCH is 18 ng. Monitoring data during the years 1970-1972 revealed a mean α-HCH concentration in ambient air of 1.2 ng/m³ in the positive samples collected across the United States (Kutz et al., 1976). Assuming an average daily intake of 20 m³ of air, this figure is equivalent to an average daily intake of 24 ng. Pertinent monitoring data regarding the other isomers of HCH could not be located in the available literature as cited in the Appendix.

A large volume of information is available concerning effects of HCH on aquatic organisms. Lindane (γ-HCH) is generally more toxic to freshwater and saltwater fish and invertebrates than other HCH isomers or mixtures (U.S. EPA, 1980b). The lowest reported acutely toxic concentrations for freshwater species were 1.7 μg/ℓ lindane, which was a 96-hour LC_{50} for brown trout (Johnson and Finley, 1980) and 1 μg/ℓ lindane, which was a 96-hour LC_{50} for stoneflies (Cope, 1965, Snow, 1958). The lowest reported acutely toxic lindane concentrations for marine fish and invertebrates, respectively, were 7.3 μg/ℓ, a 96-hour LC_{50} for striped bass (Korn and Earnest, 1974), and 0.17 μg/ℓ, a 96-hour LC_{50} for pink shrimp (Schimmel et al., 1977). Among the freshwater fishes, salmonids appeared to be more sensitive than other species. Crustaceans other than cladocerans were generally the most sensitive invertebrate species both in freshwater and saltwater (U.S. EPA, 1980b) Fish and invertebrates appeared to be about equally sensitive to HCH.

In chronic toxicity studies, no adverse effects were reported at concentrations lower than the acutely toxic levels for the most sensitive species; however, chronic toxicity data for the most acutely sensitive species were generally unavailable.

The available information indicated that aquatic plants were much less sensitive to HCH than fish or invertebrates.

HCH accumulates in aquatic biota primarily in fatty tissue; however, HCH is less lipophilic and less persistent than other organochlorines and therefore is not bioaccumulated or biomagnified to a great extent.

Two studies provide direct evidence that γ-HCH is absorbed from the gastrointestinal tract (Turner and Shanks, 1980; Ahdaya et al., 1981). The appearance of α-HCH and β-HCH in the blood and tissues after oral administration is also indicative of gastrointestinal absorption (Eichler et al., 1983; Altmann et al., 1983; Macholz et al., 1982a,b).

In general, isomers of HCH and their metabolites tend to accumulate in fatty tissue (Eichler et al., 1983; Chand and Ramachandran, 1980; Lakshmanan et al., 1979; Chadwick et al., 1978a; Altmann et al., 1983; Baumann et al., 1980; Siddiqui et al., 1981a; Szymczynski and Waliszewski, 1981a,b). In a comparative study where α-HCH or γ-HCH was fed to rats in the diet for 56 days, Eichler et al. (1983) found that α-HCH accumulated in the fat and brain to a greater extent than did γ-HCH. Furthermore, the retention of α-HCH in the tissues (fat, brain, liver, kidney) was 12-30 times greater than that of γ-HCH. Tissue concentrations of γ-HCH declined to a much greater extent than did tissue levels of α-HCH during the 15 days following termination of exposure.

The metabolism of HCH isomers primarily involves dehydrogenation, dehydrochlorination and dechlorination. Conjugation reactions with sulfuric and glucuronic acid are also important (Macholz et al., 1982a; Engst et al., 1976, 1979; Chadwick et al., 1975; Grover and Sims, 1965; Freal and Chadwick, 1973; Chadwick and Freal, 1972; Allsup and Walsh, 1982). In mammals, including humans, common metabolites of HCH include chlorinated phenols, chlorinated benzenes and pentachlorocyclohexenes. These metabolites are usually excreted in conjugated form (or a degradation product of a previously conjugated form) in the urine, and have also been detected in blood, liver, kidney, spleen, heart and brain (Engst et al., 1976; Chadwick et al., 1975, 1978a; Freal and Chadwick, 1973; Chadwick and Freal, 1972; Angerer et al., 1983; Kujwa et al., 1977; Grover and Sims, 1965). A number of _in vitro_ studies have shown that the metabolism of HCHs in mammals is mediated to a great extent by oxidative processes in hepatic microsomes (Gopalaswamy and Aiyar, 1984; Yamamoto et al., 1983; Fitzloff et al., 1982; Fitzloff and Pan, 1984; Baker et al., 1985; Tanaka et al., 1979; Portig et al., 1973).

HCH isomers and metabolites have been recovered in the urine and feces (Ahdaya et al., 1981; Kurihara et al., 1979; Chadwick et al., 1975, 1978a,b; Allsup and Walsh, 1982; Zesch et al., 1982; Angerer et al., 1981; Stein et al., 1980; Macholz et al., 1982a,b), and trace amounts (as $^{14}CO_2$) have been detected in expired air (Ahdaya et al., 1981; Chadwick et al., 1978a). In comparative studies, Kitamura et al. (1970) and Eichler et al. (1983) demonstrated that the disappearance of γ-HCH from the bodies of mice given a single oral dose or rats given repeated oral doses was more rapid than that of β-HCH or α-HCH administered in the same manner. Various isomers of HCH are known to be excreted in human milk (Herbst and Bodenstein, 1972; Welch and Findlay, 1981) and semen (Szymczynski and Waliszewski, 1981a,b).

Chadwick et al. (1978a,c) and Lakshmanan et al. (1979) have demonstrated that dietary factors (cadmium, fiber and fat) can alter the retention, metabolism and excretion of γ-HCH. Herbst and Bodenstein (1972) have suggested that lipid-mediated carriers enhance the absorption of γ-HCH. Liu (1982) suggested that the metabolism of γ-HCH might vary with the strain of animal used in the study.

Dietary α-HCH has been shown to cause increased incidences of liver tumors in five strains of mice (Ito et al., 1973a,b, 1976; Nagasaki et al., 1972a, 1975; Hanada et al., 1973; Goto et al., 1972) and in Wistar rats (Ito et al., 1975; Schulte-Hermann and Parzefall, 1981). The teratogenic and reproductive effects of α-HCH have not been investigated. Nonneoplastic hepatic changes have been observed in rats and mice fed α-HCH (Shulte-Hermann and Parzefall, 1981; Ito et al., 1973a,b, 1975, 1976; Fitzhugh et al., 1950).

Dietary β-HCH has been shown to cause increased incidences of liver tumors in CF1 and ICR-JCL mice (Thorpe and Walker, 1973; Goto et al., 1972) but not in dd mice (Ito et al., 1973a,b; Hanada et al., 1973; Nagasaki et al., 1972a) or Wistar rats (Ito et al., 1975; Fitzhugh et al., 1950). The reproductive and teratogenic effects of β-HCH have not been investigated. Nonneoplastic and neoplastic histological changes in the liver were not observed in studies that were designed to investigate hepatic carcinogenic response (Ito et al., 1973a,b, 1975); increases in absolute and relative liver weight were observed at dietary concentrations ≥250 ppm. Fitzhugh et al. (1950) observed increases in liver weight accompanied by histological changes in rats fed ≥100 ppm β-HCH; increased relative liver weight was the only effect observed at 10 ppm. Early mortality was also observed among rats fed 800 ppm. No tumors were observed in this study, though it should be noted that not all of the rats started on the test were examined histologically (no criterion for selection was given). No other chronic effects were reported.

Dietary γ-HCH was shown to cause an increased incidence of liver tumors in male CF1 mice fed 400 ppm for 110 weeks (Thorpe and Walker, 1973), and marginally in male dd mice fed 600 ppm for 32 weeks, then examined 5-6 weeks posttreatment (Hanada et al., 1973), and in male ICR-JCL mice fed 600 ppm for 26 weeks (Goto et al., 1972). No liver tumors were observed in dd mice fed up to 500 ppm for 24 weeks (Ito et al., 1973a,b; Nagasaki et al., 1972a) or in Wistar rats fed 500 ppm for up to 48 weeks (Ito et al., 1975). Significant compound-related development of tumors of any type was not observed in NMRI mice (Herbst et al., 1975; Weisse and Herbst, 1977), B6C3F1 mice (NCI, 1977), Osborne-Mendel rats (NCI, 1977) or Wistar rats (Fitzhugh et al., 1950). The study conducted by NCI (1977) has been criticized for poor survival of rats, changes in dosing regimen and the possibility that male rats did not receive MTDs (IARC, 1979). The negative findings of Fitzhugh et al. (1950) are also inconclusive since only small numbers of animals were examined histologically. The negative findings of Ito et al. (1973a,b), Nagasaki et al. (1972a) and Ito et al. (1975) might be attributed to small numbers of animals and short duration. Notably, a metabolite of γ-HCH, 2,4,6-trichlorophenol, is carcinogenic in mice and rabbits and is considered to be a probable human carcinogen (Group B2).

Orally-administered γ-HCH was not found to be teratogenic or fetotoxic in Wistar rats (Khera et al., 1979), CD rats (Palmer et al., 1978a), CFY rats (Palmer et al., 1978b), New Zealand White rabbits (Palmer et al., 1978b) or CD-1 mice (Chernoff and Kavlock, 1983; Gray and Kavlock, 1984). In contrast, a study by Dzierzawski (1977) reported increased numbers of resorbed fetuses in hamsters (40 mg/kg on day 9 of gestation), rabbits (40 or 60 mg/kg on day 9 of gestation) and rats (40, 50 or 100 mg/kg on various days of gestation). Maternal toxicity was not reported. These doses are higher than any of those tested in the negative studies of γ-HCH, though Chernoff and Kavlock (1983) reported that 25 mg/kg/day was the maximum dose that was not toxic to maternal CD-1 mice.

Palmer et al. (1978a) failed to observe adverse effects on reproduction in three generations of CD rats fed up to 100 ppm γ-HCH in the diet. Dikshith and Datta (1977) and Dikshith et al. (1978), however, observed testicular atrophy in ITRC rats gavaged with 17.6 mg γ-HCH/kg in peanut oil for 90 days, suggesting that γ-HCH might have adverse effects upon reproduction.

Long-term oral studies have shown targets for HCH toxicity to be the liver (α, γ, β) (Dikshith et al., 1978; Fitzhugh et al., 1950); Research and Consulting Co., Ltd., 1983; Oesch et al., 1982; Ito et al., 1973a, Rivett et al., 1978), kidney (α, γ) (Fitzhugh et al., 1950; Research and Consulting Co., Ltd., 1983). Hematological effects (γ) (Earl et al., 1970; Morgan et al., 1980) and neurotoxicity have also been reported (Fitzhugh et al., 1950; Czegledi-Janko and Avar, 1980). Short-term studies suggest that γ-HCH may cause immunosupression (Dewan et al., 1980; Desi et al., 1978).

Dietary δ-HCH did not cause neoplastic or nonneoplastic changes in the livers of male dd mice (Ito et al., 1973a; Nagasaki et al., 1972a) or male Wistar rats (Ito et al., 1975). These studies used small numbers of animals and were only conducted for 24 weeks. A mixture of δ- and ε-HCH caused benign and malignant hepatomas in male ICR-JCL mice when fed in the diet at 600 ppm for 26 weeks (Goto et al., 1972). Other pertinent data regarding the teratogenic, reproductive or chronic effects of δ-HCH could not be located in the available literature as cited in the Appendix.

Concerning the carcinogenicity of ε-HCH, a mixture of δ- and ε-HCH caused benign and malignant hepatomas in male ICR-JCL mice when fed in the diet at 600 ppm for 26 weeks (Goto et al., 1972). Pure ε-HCH was not evaluated. Other pertinent data regarding the health effects associated with exposure to ε-HCH could not be located in the available literature as cited in the Appendix.

T-HCH (technical grade HCH mixture) has been shown to cause increased incidences of liver neoplasms in four strains of mice (Hanada et al., 1973; Goto et al., 1972; Kashyap et al., 1979; Nigam et al., 1984a; Bhatt et al., 1981; Munir et al., 1983; Nagasaki et al., 1971, 1972b; Nagasaki, 1973; Munir and Bhide, 1984) but not in Wistar rats (Munir et al., 1983) or Syrian golden hamsters (Munir et al., 1983). T-HCH is typically 65% α isomer, 7% B, 17% γ, 4% ε and small amounts of 10 other isomers including δ.

The teratogenic effects of T-HCH have not been investigated. Nigam et al. (1979) and Shivanandappa and Krishnakumari (1981, 1983) have shown that orally-administered T-HCH causes testicular atrophy in rats and mice (≥800 ppm, rats; 500 ppm, mice).

Long-term oral administration of T-HCH has been shown to cause adverse effects on the liver (Fitzhugh et al., 1950; Barros and Saliba, 1978; Barros et al., 1982; Shivanandappa and Krishnakumari, 1981; Nigam et al., 1982, 1984a,b; Munir and Bhide, 1984), kidney (Fitzhugh et al., 1950, Barros and Saliba, 1978; Barros et al., 1982; Shivanandappa and Krishnakumari, 1981), adrenal cortex (Shivanandappa and Krishnakumari, 1981; Shivanandappa et al., 1982) and CNS (Shivanandappa and Krishnakumari, 1981; Kashyap et al., 1979). Kashyap et al. (1979) also reported that long-term oral exposure to T-HCH was associated with increased corneal opacity.

A large body of evidence indicates that the nonneoplastic changes in the liver associated with exposure to isomers of HCH or to T-HCH are associated with neoplastic development. The nonneoplastic changes support the qualitative estimation of cancer of the T-HCH mixture and the isomers of HCH that have tested positive. A clear progression of hepatic changes that ultimately lead to the development of malignant tumors has been observed at gross, histological and ultrastructural levels of examination. These nonneoplastic changes were proportional to dose and duration of HCH treatment. These liver effects are reversible only at the stages before the development of nodular hyperplasia. The exact stage at which the liver changes become irreversible has not been clearly defined (Ito et al., 1975, 1976; Schulte-Hermann and Parzefall, 1981; Munir et al., 1983; Munir and Bhide, 1984; Nigam et al., 1982, 1984a; Sugihara et al., 1975). Although nodular hyperplasia may appear to regress shortly after HCH treatment is discontinued, if the observation period is extended, the development of hepatocellular carcinoma becomes apparent (Sugihara et al., 1975). Sugihara et al. (1975) postulated that surviving cells from areas of nodular hyperplasia ultimately progress to hepatocellular carcinoma.

A q_1* of 6.34 $(mg/kg/day)^{-1}$ was derived for α-HCH, based on the combined incidences of benign and malignant liver tumors in male mice fed 0, 100, 250 and 500 ppm α-HCH in the diet in the Ito et al. (1973a) study. Corresponding concentrations of α-HCH in water associated with increased cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 5.52×10^{-5}, 5.52×10^{-6} and 5.52×10^{-7} mg/ℓ.

A $1/ED_{10}$ (F factor) of 69.5 was derived based on data for benign and malignant liver tumors in male mice fed α-HCH (Ito et al., 1973a). This F factor places α-HCH in potency Group 3 and, with an EPA classification of B2, results in a MEDIUM hazard ranking under CERCLA. A chronic toxicity-based RQ of 1000 was estimated for α-HCH, based on early mortality of rats in a chronic feeding study (Fitzhugh et al., 1950).

A q_1* of 1.8 $(mg/kg/day)^{-1}$, originally derived for β-HCH by the U.S. EPA (1982a), is the recommended value for this isomer. This q_1* is based on the combined incidence of benign and malignant liver tumors in male mice fed 0 or 200 ppm β-HCH in the diet for up to 110 weeks in the study by Thorpe and Walker (1973). Corresponding concentrations of β-HCH in water associated with increased cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 1.90×10^{-4}, 1.90×10^{-5} and 1.90×10^{-6} mg/ℓ.

A $1/ED_{10}$ (F factor) of 10.7 was derived from the data for benign and malignant liver tumors in male mice fed β-HCH (Thorpe and Walker, 1973).

This F factor places β-HCH in Potency Group 2 and with an EPA classification of C, results in a LOW hazard ranking under CERCLA. A chronic toxicity-based RQ of 1000 was based on early mortality of rats in a chronic feeding study with β-HCH (Fitzhugh et al., 1950).

A q_1^* of 1.3 $(mg/kg/day)^{-1}$, which was derived for γ-HCH by the U.S. EPA (1980a), remains the recommended value. This q_1^* is based on the combined incidence of benign and malignant liver tumors in male mice fed 0 or 400 ppm γ-HCH in the diet for 110 weeks in a study by Thorpe and Walker (1973). Corresponding concentrations of γ-HCH in water associated with increased cancer risks of 10^{-5}, 10^{-6} and 10^{-7} are 2.64×10^{-4}, 2.64×10^{-5} and 2.64×10^{-6} mg/ℓ.

A $1/ED_{10}$ (F factor) of 7.4 was derived from the data for benign and malignant liver tumors in male mice fed γ-HCH (Thorpe and Walker, 1973). This F factor places γ-HCH in Potency Group 3 and, with an EPA classification between B2 and C, results in a MEDIUM to LOW hazard ranking under CERCLA. The chronic toxicity-based RQ for γ-HCH, based on degenerative changes in the kidneys of rats in a subchronic oral study (Research and Consulting Co., Ltd., 1983), is 100.

Pertinent data for the derivation of an RfD or RQ or for assessing carcinogenicity were not available for δ- or ε-HCH. Both these isomers are given EPA classifications of C. Since it was not possible to derive a potency estimate, a default potency group of 2 is assigned. A Group C weight-of-evidence combined with a Group 2 potency results in a LOW hazard ranking under CERCLA.

A q_1^* of 1.76 $(mg/kg/day)^{-1}$ was derived for T-HCH from the combined incidences of benign and malignant liver tumors in male mice fed 0, 125 and 250 ppm T-HCH in the diet from 8-10 weeks of age until 15-17 months of age

(Munir et al., 1983). Corresponding concentrations of T-HCH in water associated with increased cancer risk levels of 10^{-5}, 10^{-6} and 10^{-7} are 1.99×10^{-4}, 1.99×10^{-5} and 1.99×10^{-6} mg/ℓ.

A $1/ED_{10}$ (F factor) of 8.1 was calculated from the data for benign and malignant liver tumors in male mice fed T-HCH as noted above (Munir et al., 1983). The animal evidence for T-HCH is sufficient, thus an EPA Group B2 weight-of-evidence classification. A chronic toxicity-based RQ of 100 was estimated for T-HCH on the basis of histological and histochemical adrenal changes indicative of steroidogenic inhibition in rats in a subchronic oral study (Shivanandappa et al., 1982).

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LIST OF ABBREVIATIONS

AchE	Acetylcholinesterase
ADI	Acceptable daily intake
ATP	Adenosine triphosphate
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
EC_{50}	Concentration effective to 50% of recipients
EEG	Electroencephalogram
FEL	Frank-effect level
HCH	Hexachlorocyclohexane
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol/water partition coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MATC	Maximum acceptable toxicant concentration
MED	Minium effective dose
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEC	No-observed-effect concentration

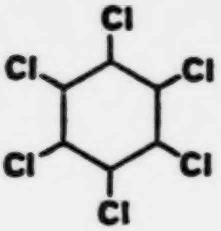
LIST OF ABBREVIATIONS (cont.)

PCB	Polychlorinated biphenyls
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per thousand
RBC	Red blood cell
RNA	Ribonucleic acid
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
SDH	Succinic dehydrogenase
T-HCH	Technical grade HCH
TWA	Time-weighted average
UDP	Uridine diphosphate
UV	Ultraviolet

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

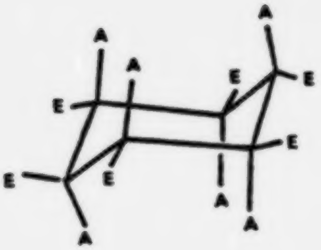
The structure of HCH is depicted below.



Molecular weight: 290.7

Empirical formula: $C_6H_6Cl_6$

The orientations of the various isomers discussed in this document are given below. The CAS numbers of the possible HCH isomers are listed in Table 1-1.



Orientation of Cl Atoms on Ring	Isomer	Percent of Isomer in Technical HCH
AAEEEE	α	60-70
EEEEEE	β	5-12
AAAEEE	γ (lindane)	10-15
AEEEEE	δ	6-10
AEEAEE	ε	3-4

1.2. PHYSICAL AND CHEMICAL PROPERTIES

The isomers of HCH are white or yellowish powders or flakes, depending on the isomer. The odor also depends on the isomer. The isomers are soluble in 100% alcohol, chloroform or ether (Hawley, 1981). Selected physical properties are listed in Table 1-1.

HCH isomers can be decomposed by alkaline substances (Hawley, 1981), and can undergo reactions typical of alkyl halides, including hydrolysis and dehydrohalogenation (Morrison and Boyd, 1973).

TABLE 1-1

CAS Numbers and Physical Properties of HCH Isomers

Isomer	CAS Number	Melting Point (°C)	Boiling Point (°C)	Specific Gravity	Vapor Pressure (mm Hg)	Water Solubility (mg/ℓ)	Log K_{ow}	Henry's Law Constant (atm·m³/mol)	Isomer Conformation[a]
γ-HCH	58-89-9	112[b] 112.5[e]	NR	1.87[c]	9.4×10^{-6} (20°C)[b] 0.14 (40°C)[e]	7.5 (25°C)[b]	3.72[b]	4.8×10^{-7}[d]	aaaeee
α-HCH	319-84-6	157-158[b]	decomposes at 288°C	1.87[c]	2.5×10^{-5} (20°C)[b]	2.0 (25°C)[b]	3.81[b]	4.8×10^{-6}[d]	aaeeee
β-HCH	319-85-7	309[b]	sublimes[b]	1.87[c]	2.8×10^{-7} (20°C)[b]	0.24 (25°C)[b]	3.80[b]	4.5×10^{-7}[d]	eeeeee
δ-HCH	319-86-8	138-139[b]	NR	1.87[c]	1.7×10^{-5} (20°C)[b]	31.4 (25°C)[b]	4.14[b]	2.1×10^{-7}[d]	aeeeee
ε-HCH	6108-10-7	218.2[a]	NR	NR	NR	17.4[d]	4.14	2.1×10^{-7}	aeeaee

[a] Colson, 1979

[b] U.S. EPA, 1981

[c] Hawley, 1981

[d] Lyman et al., 1982

[e] Windholz, 1983

a = Axial; e = equatorial; NR = not reported

1.3. PRODUCTION DATA

Production data from the 1977 TSCA Inventory (U.S. EPA, 1977) are presented in Table 1-2.

T-HCH (65:7:14:4:10; α, β, γ, ε, other isomers) is produced by the action of visible or UV light, X-rays or gamma rays on a mixture of benzene and chlorine in the presence of free radical initiators. Batch or continuous methods in stirred tank type reactors or tubular reactors are used. Typically, benzene in excess is chlorinated at 15-25°C at 1 atm in a glass reactor. Oxygen and substitution catalysts such as iron must be excluded. Part of the benzene is removed at ambient pressure with the remaining benzene being removed at reduced pressure. The molten product is then steam stripped to remove residual traces of benzene (Colson, 1979).

Lindane, which is >99% γ-HCH, is produced commercially by the supersaturation process or the fluid classification process. After α-HCH is supersaturated in a lower primary alcohol such as methanol, leaving most of the γ-HCH undissolved, the alcohol is removed, and the γ-HCH-rich material is then dissolved in carbon tetrachloride or a paraffinic hydrocarbon. A γ-HCH rich concentrate is precipitated from this preparation. The concentrate from which the very pure γ-HCH is finally isolated contains a number of impurities including α-, β- and δ-HCH and other minor impurities. The δ-HCH and minor impurities are removed by the preparation of a saturated solution consisting of the α-, β- and γ-HCH isomers. Methanol or isopropanol are the solvents of choice for this step. The α- and β-HCH isomers form smaller crystals than does γ-HCH, so careful decantation of the mixture of HCH crystals leads to a very pure preparation of γ-HCH. Virtually all the lindane produced in the United States is produced in this manner (Colson, 1979). No information was available on the fluid classification process.

TABLE 1-2

Production Data for HCH*

Isomer	Company/Location	Importer/ Manufacturer	Production Range (lbs)
γ-HCH	Steuber Co., Inc. New York, NY	importer	10,000-100,000
	Napp Chemicals, Inc. Lodi, NJ	importer	1,000-10,000
	Hooker Chemicals & Plastics Niagara Falls, NY	manufacturer	NR
α-HCH	Hooker Chemicals & Plastics Niagara Falls, NY	manufacturer	NR
β-HCH	Hooker Chemicals & Plastics Niagara Falls, NY	manufacturer	NR
δ-HCH	Hooker Chemicals & Plastics Niagara Falls, NY	manufacturer	NR
ε-HCH	Hooker Chemicals & Plastics Niagara Falls, NY	manufacturer	NR

*Source: U.S. EPA, 1977

NR = Not reported

1.4. USE DATA

γ-HCH is used as an insecticide on hardwood logs and lumber, seeds (such as wheat, oats and rye, corn, sorghum, lentils, dry peas), vegetables and fruits (such as avocados, pineapples, curcubits, pecans), woody ornamentals (such as Christmas trees), hardwood forests, livestock and pets (external parasite control) and existing structures (control for woodboring beetles and termites) (Federal Register, 1983). Pertinent data regarding uses of the remaining isomers in a pure state could not be located in the available literature as cited in the Appendix. The technical form of HCH contains all the isomers, however, and has been used as an insecticide in the past. It is no longer used as such in the United States (Colson, 1979).

1.5. SUMMARY

The isomers of HCH are white or yellowish powders or flakes, with differing odors depending on the isomer. The isomers are soluble to varying degrees in a variety of organic solvents including ethyl alcohol, chloroform, acetone, dioxane, ether and others (Colson, 1979). HCHs can be decomposed by alkaline substances and are expected to undergo reactions typical of alkyl halides including hydrolysis and dehydrohalogenation (Morrison and Boyd, 1973).

T-HCH, a 65:7:17:4:10 mixture of α, β, γ, ε and other isomers of HCH, respectively, is produced by the photochemically-induced reaction between benzene and chlorine in the presence of a free radical initiator. A variety of physical separation methods are used to purify γ-HCH to 99.9% from T-HCH for use as an insecticide (lindane) (Colson, 1979).

γ-HCH is used as an insecticide on hardwood logs and lumber, a variety of seeds, vegetables and fruits, woody ornamentals including Christmas trees, hardwood forests, livestock and pets (external parasite control) and existing structures (control of woodboring beetles and termites) (Federal Register, 1983). Pertinent data regarding uses of the other isomers in the pure state could not be located in the available literature as cited in the Appendix. The technical product has been used as an insecticide in the past but is no longer used as such (Colson, 1979).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Hydrolysis rate constants at 25°C of 7.5×10^{-3}, 8.99×10^{-4} and 1.07×10^{-3} $hour^{-1}$ were determined for γ-HCH in surface water samples from a eutrophic pond in Texas (pH 9.3), a dystrophic reservoir in Louisiana (pH 7.3) and an oligotrophic rock quarry in Indiana (pH 7.8), respectively (Saleh et al., 1982). The corresponding hydrolysis half-lives are 92, 771 and 648 hours. Hydrolysis rates of 7.4×10^{-4}, 1.6×10^{-4} and 7.3×10^{-3} $hour^{-1}$ at pH values of 5, 7 and 9, respectively, were observed for γ-HCH in Milli-Q water at 25°C (Saleh et al., 1982). The hydrolysis reactions followed first-order kinetics. Hydrolysis in acidic or neutral waters is not expected to be a significant fate process for γ-HCH, although alkaline hydrolysis may be important.

Pertinent data regarding the rate of hydrolysis of α-HCH could not be located in the available literature as cited in the Appendix. Hydrolysis of γ-HCH has been observed, however, and based on the relatively greater stability of α-HCH imparted by its greater number of equatorial chlorines, it may hydrolyze more slowly than γ-HCH.

Pertinent data regarding the hydrolysis of any of the other isomers of HCH could not be located in the available literature as cited in the Appendix. β-, δ- and ε-HCH, however, have more equatorial chlorines than γ-HCH, and since equatorial bonds are generally more stable than axial bonds, it is expected that these isomers will be more resistant to hydrolysis than γ-HCH.

2.1.2. Oxidation. Pertinent data regarding the oxidation of any of the isomers of HCH could not be located in the available literature as cited in the Appendix.

2.1.3. **Photolysis.** First-order photolysis of γ-HCH was observed in direct sunlight photolysis experiments in water samples from a eutrophic pond in Texas, a dystrophic reservoir in Louisiana and an oligotrophic rock quarry in Indiana (Saleh et al., 1982). The photolysis rate constants were 4.1×10^{-3} (Texas), 3.9×10^{-4} (Louisiana) and 4.5×10^{-4} (Indiana) hour^{-1}, which correspond to photolysis half-lives of 169, 1791 and 1540 hours, respectively. The relatively low half-life value observed in the Texas water samples was attributed to the higher pH since the products of hydrolysis, which were presumably in equilibrium with γ-HCH, were reported to be more susceptible to photolysis than γ-HCH. A dark control was used in these studies (Saleh et al., 1982). After 50 days exposure to sunlight, the concentration of γ-HCH in purified water dropped from ~9300 to ~7600 µg/mℓ, and the concentration of α-HCH dropped from ~1480 to ~1130 µg/mℓ (Malaiyandi et al., 1982). Since γ-HCH and α-HCH have no conjugated unsaturated systems, it is difficult to explain these apparent photolyses. It is expected, however, that direct photolysis will not be a predominant fate mechanism for γ-HCH or α-HCH in the environment.

Pertinent data regarding the photolysis of any of the other isomers of HCH could not be located in the available literature as cited in the Appendix. These compounds are not expected to absorb radiation of wavelengths present in sunlight since they do not have conjugated unsaturated systems. They should not, therefore, directly photolyze in the environment.

2.1.4. **Microbial Degradation.** Of the γ-HCH added to unsterilized natural waters in capped bottles, <30% remained after 16 weeks (Sharom et al., 1980). The authors concluded that biodegradation was responsible for this result, although it was unclear to what extent hydrolysis may have been involved. About 25% of γ-HCH in raw wastewater from Cincinnati was removed during aerobic biodegradation in a wastewater treatment plant (Petrasek et al., 1983). Aqueous biodegradation data were not available for any of the other isomers of HCH.

2.1.5. **Miscellaneous Processes.** The isomerization of γ-HCH to α-HCH by sunlight has been reported (Malaiyandi et al., 1982). Only a small amount of γ-HCH is affected by this transformation, however, so it is not expected to be a major environmental fate process.

Deo et al. (1980) observed the formation of α-, γ- and δ-HCH by the reaction of β-HCH with water at 25°C. Only a small portion (not quantified) of the β-HCH was transformed, however, so the process is not a major fate process for β-HCH. Instantaneous dechlorination of β-HCH was also observed (Deo et al., 1980).

2.1.6. Transport.

2.1.6.1. **VOLATILIZATION** -- Assuming a depth of 1 m, the volatilization half-life of γ-HCH from water has been estimated to be 115 days (Lyman et al., 1982) and 191 days (Mackay and Leinonen, 1975). From a depth of 4.5 cm, a volatilization half-life of 3.2 days was determined for γ-HCH in still, pure water at 24°C, while with stirring, the half-life was 1.5 days (Chiou et al., 1980). Using an equation relating water depth to volatilization half-life (Chiou et al., 1980), the experimental volatilization half-life of 3.2 days was used to calculate a half-life of 692 days for a depth of 1 m. Since this figure is of the same order of magnitude as the estimated half-lives of 115 and 191 days for volatilization from 1 m, these figures are considered to be valid estimates of the tendency of lindane to volatilize.

Measured values of the water solubilities and vapor pressures of the HCH isomers (except ε-HCH) were used to estimate the Henry's Law constants of the isomers that are presented in Table 1-1. Because no experimental data were available for ε-HCH, the Henry's Law constant for δ-HCH, the isomer which most closely resembles ε-HCH, is given in Table 1-1 as an estimate of the ε-HCH Henry's Law constant. Based on these values, all the isomers of HCH are expected to volatilize from water at a rate dependent upon the rate of diffusion through the air (Lyman et al., 1982).

2.1.6.2. ADSORPTION -- A mean K_{oc} of 1080.9 was obtained for γ-HCH from K_{oc} determinations on three soils with an average organic content of 13% (Rao and Davidson, 1982). Based on this moderate K_{oc} value and a water solubility of 7.5 ppm (U.S. EPA, 1981), γ-HCH is expected to leach slowly to groundwater. The leaching of γ-HCH from Gezira soil (38.8% sand, 34.7% silt, 26.2% clay and 4.6% organic carbon) from the Sudan was slow; after 45 days, <50% of the applied γ-HCH had leached from the soil (El Beit et al., 1981). The fate of γ-HCH has been studied in a field scale experiment (Di Toro and Paquin, 1984). After 100 days, 75% of the applied γ-HCH was found in the water column and sediment layer of the rock quarry; the water column contained >75% of this amount. The role of particle transport in the transfer of γ-HCH to the sediment was found to be small compared with diffusion (Di Toro and Paquin, 1984). Saleh et al. (1982) determined Freundlich constants for γ-HCH sorption and desorption for four systems: montmorillonite clay-distilled water, 1258.9 for both sorption and desorption; Roselawn Cemetery water-sediment, 354.8 and 4.26; Cross Lake water-sediment, 56.2 and 11,220.2; and Indiana Quarry water-sediment, 2238.7 and 4.26 for sorption and desorption, respectively. Saleh et al. (1982) reported that the high desorption constant for the Cross Lake system suggested a strong interaction between γ-HCH and the organic material in the samples, although the organic contents of the two sediment samples were similar (Roselawn Cemetery, 1.34% and Cross Lake, 1.33%).

Using a measured water solubility of 2.0 mg/ℓ (U.S. EPA, 1981), a K_{oc} of 6463 was estimated for α-HCH (Lyman et al., 1982). According to Kenaga (1980), a K_{oc} of $\geq$1000 indicates such strong adsorption to organic matter in soil that the compound is considered immobile. The K_{oc} value of α-HCH and its low water solubility, therefore, suggest that α-HCH will bind tightly to soil and leach slowly to groundwater.

A log K_{oc} value of 3.46 was determined for β-HCH (Schwarzenbach and Westall, 1981). The water solubility of β-HCH is 0.24 mg/ℓ (U.S. EPA, 1981), and combined with the log K_{oc} of 3.46, β-HCH is expected to bind tightly to soil (Kenaga, 1980) and leach slowly to groundwater.

Using a measured water solubility of 31.4 mg/ℓ (U.S. EPA, 1981), a K_{oc} of 1394.3 was estimated for δ-HCH (Lyman et al., 1982). The moderate water solubility and K_{oc} of δ-HCH suggest that the isomer will bind less tightly than the previous isomers, but still tightly enough to prevent rapid infiltration to groundwater.

Since a measured water solubility for ε-HCH was not available, the measured K_{ow} of δ-HCH, the isomer that most resembles ε-HCH, was used to estimate a water solubility of 17.4 mg/ℓ for ε-HCH, which was then used to estimate a K_{oc} value of 1950. The estimated water solubility and K_{oc} values suggest that ε-HCH will bind fairly tightly to soil and will slowly leach to groundwater.

2.1.6.3. **BIOACCUMULATION** -- Direct introduction of γ-HCH to water along with the primary food organism (yeast) resulted in a BCF of 183 in brine shrimp, while introduction of γ-HCH onto sand resulted in a BCF in the shrimp of 95. Exposure of northern brook silverside fish to γ-HCH residues on sand resulted in a BCF of 1613 (Matsumura and Benezet, 1973).

An average BCF of 319 for γ-HCH was observed in *Salmo gairdneri* Richardson fry (Ramamoorthy, 1985). BCF factors of 1246 in topmouth gudgeons (Kanazawa, 1983), 560 in the fish, *Gambusia affinis* (Schimmel et al., 1977) and 456 in the snail, *Physa* (Metcalf et al., 1973) were observed. Mean BCF values of 84, 218, 63 and 490 were determined for pink shrimp, pinfish, grass shrimp and sheepshead minnows, respectively (Schimmel et al., 1977). A BCF of 697 was observed for γ-HCH in short-necked clams (Yamoto et al., 1983).

BCFs of 161 in short-necked clams (Yamato et al., 1983), 706 in guppies (Yamato et al., 1983), 216 in the golden orfe, 586 in guppies, 330 in carp and 605 in brown trout (Sugiura et al., 1979) were reported for α-HCH. Yamato et al. (1983) observed BCFs of 1043 and 127 for β-HCH and 648 and 272 for δ-HCH in guppies and short-necked clams, respectively.

Pertinent data regarding the bioconcentration of ε-HCH could not be located in the available literature as cited in the Appendix. It is expected, however, that ε-HCH will bioconcentrate to a similar extent as δ-HCH because the two isomers are similar. Bioconcentration is not expected to be significant for any of the isomers of HCH.

2.1.7. Persistence. Based on degradation data, the persistence half-lives for γ-HCH in river, lake and groundwater were estimated to be 3-30, 30-300 and >300 days, respectively (Zoeteman et al., 1980). Pertinent data regarding the persistence of the other HCH isomers could not be located in the available literature as cited in the Appendix.

2.2. AIR

2.2.1. Chemical Removal Processes. The half-life of the reaction of HCH (unspecified isomer) with hydroxyl radicals in the atmosphere was estimated to be 1.63 days (U.S. EPA, 1985a).

2.2.2. Physical Removal Processes. The removal rates of γ-HCH from the atmosphere by rainfall and dry deposition are 2.5 and 3.3% per week, respectively, and the estimated residence time of γ-HCH in the atmosphere is 17 weeks (Lewis and Lee, 1976). Pertinent data regarding the removal of the other isomers of HCH could not be located in the available literature as cited in the Appendix.

2.3. SOIL

2.3.1. Microbial Degradation. As the sole carbon source, γ-HCH was found to support the growth of 71/147 microorganisms isolated from loamy sand (Tu, 1976). Chloride ion formation was noted in these cultures. The extent of biodegradation in these pure culture studies was not given. Metabolites isolated from 13 of the 71 microorganisms included γ-2,3,4,5,6-pentachloro-1-cyclohexene, α-, β- and γ-3,4,5,6-tetrachloro-1-cyclohexene and pentachlorobenzene (Tu, 1976). From moist aerated soil, 62% of the applied γ-HCH was recovered and 3% of the applied ^{14}C was released after 105 days. After 140 days, 17.8% of the applied ^{14}C was released from submerged soil. The loss of γ-HCH from submerged anaerobic soil measured by gas-liquid chromatography was nearly quantitative, with only 4% of the applied γ-HCH recoverable (Kohnen et al., 1975). Mathur and Saha (1975) reported that 1,2,4-trichlorobenzene, 1,2,3,4-tetrachlorobenzene, γ-2,3,4,5,6-pentachlorocyclohex-1-ene and γ-3,4,5,6-tetrachloroclohexane were detected by gas chromatography in the soil 6 weeks after it was treated with γ-HCH and submerged. The absence of these products from sterilized soil treated with γ-HCH was cited as evidence that the compounds were metabolic products from γ-HCH biodegradation. Incubation of aerobic and anaerobic soil suspensions of γ-HCH for 3 weeks resulted in the disappearance of zero and 63.8% of the applied γ-HCH, respectively (Lichtenstein et al., 1971), indicating that anaerobic degradation of γ-HCH is more extensive than aerobic degradation. A *Clostridium* sp. isolated from γ-HCH-amended soil was observed to degrade 87% of added γ-HCH in 24 hours under anaerobic conditions (Sethunathan and Yoshida, 1973). Biodegradation of γ-HCH in thick anaerobic digested wastewater sludge at 35°C was rapid, with <10% of the added 10 and 1 ppm γ-HCH remaining after 2 and 4 days, respectively (Hill and McCarty, 1967). When γ-HCH was added to an anaerobic preparation of *Citrobacter freundii*, *Clostridium butyricum*, *Clostridium pasteurianum* or mixed soil flora, 91.5, 98.3, 91.0 and 78.0% of the organic ^{35}Cl was released as ^{35}Cl ion (Haider, 1979). Several studies have shown that anaerobic microbial action can transform γ-HCH into α-HCH (Vonk and Quirijns, 1979; Engst et al., 1979). This conversion is not extensive, however, and is not expected to be of major importance in the fate of γ-HCH.

After 2 weeks in unsterilized submerged Casiguran sandy loam, the concentration of α-HCH declined from ~16 to <1 ppm compared with a decline from ~18 to 15 ppm in a sterilized preparation (Castro and Yoshida, 1974). In another experiment, incubation of aerobic and anaerobic soil suspensions of α-HCH for 3 weeks resulted in the disappearance of 11.0 and 26.2% of the added α-HCH, respectively (MacRae et al., 1984), indicating that anaerobic degradation is more extensive than aerobic biodegradation. Anaerobic pure cultures, probably *Clostridium* sp., degraded suspensions of α-HCH in flooded soils, although no information on rates was given (Ohisa and Yamaguchi, 1978). When α-HCH was added to an anaerobic preparation of *C. freundii*, *C. butyricum*, *C. pasteurianum* or mixed soil flora, 13.9, 97.4, 53.2 and 6.5% of the organic ^{35}Cl was released as ^{35}Cl ion (Haider, 1979). After 20 weeks of aerobic and anaerobic incubation of soil samples polluted with α-HCH, 55 and 35% of the initial amount of α-HCH had biodegraded (Doelman et al., 1985).

When β-HCH and δ-HCH were added to an anaerobic preparation of *C. freundii*, *C. butyricum*, *C. pasteurianum* or mixed soil flora, 15.3, 23.8, 10.1 and 7.4% (β-HCH), respectively, and 2.8, 38.5, 5.0 and 1.6% (δ-HCH), respectively, of the organic ^{35}Cl was released as ^{35}Cl ion (Haider, 1979). Pertinent data regarding the biodegradation of ε-HCH could not be located in the available literature as cited in the Appendix.

2.3.2. Photolysis. Pertinent data regarding the photolysis of HCH isomers in soil could not be located in the available literature as cited in the Appendix. Although some data suggest that γ-HCH is subject to photolysis in water (Saleh et al., 1982), because the lack of a conjugated unsaturated system indicates that little or no absorption of light should occur in the environment, soil photolysis is not expected to be significant.

2.3.3. Adsorption-Leaching. A mean K_{oc} of 1080.9 was obtained from K_{oc} determinations on three soils with an average organic content of 13% (Rao and Davidson, 1982). Based on this moderate K_{oc} value and a water solubility of 7.5 ppm (U.S. EPA, 1981), γ-HCH is expected to leach slowly to groundwater. The leaching of γ-HCH from Gezira soil (38.8% sand, 26.2% clay and 4.6% organic carbon) from the Sudan was slow; after 45 days, <50% of the applied γ-HCH had leached from the soil (El Beit et al., 1981). Fifteen years following the application of technical HCH to a sandy loam soil in Nova Scotia, Canada, 4, 44, 10 and 14% of the applied α-, β-, γ- and δ-HCH remained in the soil, respectively. Of this amount, ~92, 92.1, 94.7 and 95.1% of the α-, β-, γ- and δ-HCH was found within a depth of 0-20 cm, indicating minimal leaching of the isomers. The soil was cultivated yearly throughout the 15-year period, increasing the likelihood that volatilization may have occurred (Stewart and Chisholm, 1971).

Using a measured water solubility of 2.0 mg/ℓ (U.S. EPA, 1981), a K_{oc} of 6463 was estimated for α-HCH (Lyman et al., 1982). According to Kenaga (1980), a K_{oc} of $\geq$1000 indicates such strong adsorption to organic matter in soil that the compound is considered immobile. The K_{oc} value of α-HCH and its low water solubility, therefore, suggest that α-HCH will bind tightly to soil and leach slowly to groundwater.

Schwarzenbach and Westall (1981) determined a log K_{oc} value of 3.46 for β-HCH. Using the water solubility for β-HCH of 0.24 mg/ℓ (U.S. EPA, 1981) and the log K_{oc} of 3.46, β-HCH is expected to bind tightly to soil (Kenaga, 1980) and leach slowly to groundwater.

Using a measured water solubility of 31.4 mg/ℓ (U.S. EPA, 1981), a K_{oc} of 1394.3 was estimated for δ-HCH (Lyman et al., 1982). The moderate water solubility and K_{oc} suggest that the isomer will bind less tightly than the previous isomers, but still tightly enough to prevent rapid infiltration to groundwater.

Since a measured water solubility for ε-HCH was not available, the measured K_{ow} for δ-HCH, the isomer that most resembles ε-HCH, was used to estimate a water solubility of 17.4 mg/ℓ for ε-HCH, which was then used to estimate a K_{oc} value of 1950. The water solubility and K_{oc} values suggest that ε-HCH will bind fairly tightly to soil and will slowly leach to groundwater.

2.3.4. Volatilization. After 50 hours, 26 and 100% of surface applied γ-HCH remained on Hatboro silt loam and Norfolk sandy loam, respectively (Glotfelty et al., 1984). The authors concluded that γ-HCH did not volatilize on the sandy loam because of the dryness of the soil. From a moist soil surface, the γ-HCH content decreased to 50 and 10% of the amount applied after 6 hours and 6 days, respectively, while 50 hours after the application of γ-HCH to dry soil, 88% of the applied compound remained (Glotfelty et al., 1984). The γ-HCH content of fallow soil in a micro-agroecosystem chamber declined to 12% of that applied after 11 days (Nash, 1983).

Pertinent data regarding volatilization of the other HCH isomers could not be located in the available literature as cited in the Appendix. The estimated Henry's Law constants, K_{oc}s and measured water solubilities (see Table 1-1) suggest that the isomers will bind fairly tightly to soil and will have little tendency to volatilize from dry soils. Volatilization from moist soils, however, may be significant.

2.4. SUMMARY

Half-lives of γ-HCH in water at 25°C were reported to be 92, 771 and 648 hours in natural water samples from a eutrophic pond in Texas (pH 9.3), a dystrophic reservoir in Louisiana (pH 7.3) and an oligotrophic rock quarry in Indiana (pH 7.8), respectively (Saleh et al., 1982). Hydrolysis experiments in Milli-Q water at pH values of 5, 7 and 9 yielded half-lives of 936, 4331 and 95 hours, respectively (Saleh et al., 1982). Therefore, hydrolysis at alkaline pH values is expected to be important in the fate of γ-HCH, while hydrolysis at acidic and neutral pH values is not. Pertinent data regarding the hydrolysis of the other isomers of HCH could not be located in the available literature; however, all these isomers contain more equatorial bonds than γ-HCH, and since these bonds are generally more stable than axial bonds, it is expected that the remaining isomers will be more stable to hydrolysis than γ-HCH.

First-order photolysis half-lives for γ-HCH of 169, 1791 and 1540 hours were observed in natural water samples from a eutrophic pond in Texas, a dystrophic reservoir in Louisiana and an oligotrophic rock quarry in Indiana, respectively (Saleh et al., 1982). The relatively short photolysis half-life observed in the Texas sample was attributed to the alkaline pH that, it was concluded, generated hydrolysis products more susceptible to photolysis than γ-HCH (Saleh et al., 1982). After 50 days exposure to sunlight, the concentrations of γ- and α-HCH in purified water dropped from ~9300 to ~7600 μg/mℓ and from 1480 to ~1130 μg/mℓ, respectively (Malaiyandi et al., 1982). Pertinent data regarding the photolysis of the other HCH isomers could not be located in the available literature as cited in the Appendix. Direct photolysis, however, is not expected to be a major fate process for any of the HCH isomers since they do not have conjugated unsaturated systems.

Of the γ-HCH added to unsterilized natural waters in capped bottles, <30% remained after 16 weeks (Sharom et al., 1980). About 25% of the γ-HCH in raw wastewater from Cincinnati was removed during aerobic biodegradation in a wastewater treatment plant (Petrasek et al., 1983). Pertinent data regarding the aqueous biodegradation of the other HCH isomers could not be located in the available literature as cited in the Appendix.

Malaiyandi et al. (1982) reported that a small amount of γ-HCH isomerized to α-HCH upon exposure to sunlight. β-HCH reacts with water at 25°C to form small amounts of α-, δ- and γ-HCH, and instantaneous dechlorination of β-HCH in water was observed to a small degree (Deo et al., 1980). None of these processes are expected to contribute significantly to the degradation of the HCH isomers in the environment.

The volatilization half-life of γ-HCH has been estimated to be 115 days (Lyman et al., 1982) and 191 days (Mackay and Leinonen, 1975), assuming a depth of 1 m. Volatilization half-lives of 3.2 and 1.5 days were observed for γ-HCH from still and stirred water 4.5 cm deep (Chiou et al., 1980). The measured volatilization half-life of 3.2 days was used to estimate a half-life of 692 days from water 1 m deep. Since the half-lives of 115 and 191 days are of the same order of magnitude as the half-life estimated from experimental data, the former values are considered to be accurate estimates of the tendency of q-HCH to volatilize. Henry's Law constant values for the other isomers have been estimated and suggest that volatilization of all HCH isomers occurs at a rate dependent upon the rate of diffusion through the air (Lyman et al., 1982). Volatilization of HCH isomers in water is not expected to be significant in the environment.

A mean K_{oc} for γ-HCH of 1080.9 was obtained from K_{oc} determinations on three soils (Rao and Davidson, 1982). Based on this K_{oc} and a low water solubility of 7.5 ppm (U.S. EPA, 198), γ-HCH is expected to leach slowly to groundwater. K_{oc} values for the remaining HCH isomers were estimated (Lyman et al., 1982), and combined with the fairly low water solubilities of the isomers suggest that they are expected to bind fairly tightly to soil and to leach slowly to groundwater. Fifteen years following the application of technical HCH to a sandy loam soil in Canada, >90% of the applied α-, β-, γ- and δ-HCH remained in the upper 20 cm of soil, indicating minimal leaching had taken place (Stewart and Chisholm, 1971).

BCFs for γ-, α-, β- and δ-HCH in a variety of species ranged from 63-1613 (Matsumura and Benezet, 1973; Ramamoorthy, 1985; Kanazawa, 1983; Schimmel et al., 1977; Metcalf et al., 1973; Yamato et al., 1983; Sugiura et al., 1979). No BCF values were available for ε-HCH, but is expected to bioaccumulate similarly to δ-HCH, to which it bears a close structural similarity. None of the HCH isomers are expected to bioconcentrate significantly in aquatic organisms.

Based on degradation data, the persistence half-lives for γ-HCH in river, lake and groundwater were estimated to be 3-30, 30-300 and >300 days, respectively (Zoeteman et al., 1980). Pertinent data regarding the persistence of the other isomers could not be located in the available literature as cited in the Appendix.

Anaerobic soil preparations were found to readily degrade γ-HCH (Kohnen et al., 1975; Mathur and Saha, 1975; Lichtenstein et al., 1971; Sethunathan and Yoshida, 1973; Haider, 1979). Degradation of α-HCH by anaerobic soils has also been observed (Castro and Yoshida, 1974; MacRae et al., 1984; Haider, 1979). Doelman et al. (1985) observed greater aerobic than anaerobic degradation of α-HCH in polluted soil. Anaerobic degradation of α-, β- and δ-HCH by several organisms has been observed (Haider, 1979). Pertinent data regarding the biodegradation of ε-HCH could not be located in the available literature as cited in the Appendix.

After 50 hours, 26 and 100% of the surface applied γ-HCH remained on Hatboro silt loam and Norfolk sandy loam, respectively (Glotfelty et al., 1984). The low volatility of the γ-HCH was attributed to the dryness of the sandy loam. From a moist soil surface, the γ-HCH content decreased to 50 and 10% of the amount applied after 6 hours and 6 days, respectively, while 50 hours after the application of γ-HCH to dry soil, 88% of the applied compound remained (Glotfelty et al., 1984). Pertinent data regarding the volatilization of the other HCH isomers could not be located in the available literature as cited in the Appendix. The estimated Henry's Law constants, K_{oc} and measured water solubility values suggest that the isomers will bind fairly tightly to soil and will have little tendency to volatilize from dry soils. Volatilization from moist soils, however, may be significant.

3. EXPOSURE

3.1. WATER

γ-HCH has been detected at 0.01 ppb in Cincinnati, OH, drinking water (Keith et al., 1976). Rural potable water samples in Hampton County, SC, ranged from not detected (<10 ppt) to 319 ppt, with a median concentration of 10 ppt, and in Chesterfield County, SC, from not detected to 193 ppt, with a median concentration of 10 ppt. Median γ-HCH concentrations in closed wells in Chesterfield and Hampton Counties were 16 and 163 ppt, respectively, and in Hampton County open wells, was 98 ppt (Sandhu et al., 1978). Potable water samples from Oahu, HI, contained 0.06-0.4 ppt γ-HCH, with a mean concentration of 0.2 ppt (Bevenue et al., 1972). Tap water from Ottawa, Ontario contained 1.3 μg/ℓ γ-HCH (Kraybill, 1977). Using 2 ℓ as the average amount of water consumed daily, the average daily intake of γ-HCH from water consumption ranges from 0.02-0.638 μg, based on the monitoring data (excluding the data from Ottawa) above; based on the concentration of γ-HCH in the Ontario tap water, the average daily intake is 2.6 μg. Since the monitored value of the γ-HCH concentration is so high relative to all the other values, this intake value is considered to be nonrepresentative. Residues of γ-HCH in whole samples of Oregon river water (includes dissolved and suspended γ-HCH) ranged from <0.001-0.002 μg/ℓ (U.S. EPA, 1985a). Surface water from Niagara-on-the-Lake (Oliver and Charlton, 1984), Washington, DC and Denver, CO (Cole et al., 1984), Virginia (Saleh et al., 1982), South Carolina (Sandhu et al., 1978), Hawaii (Bevenue et al., 1972) and New Jersey (Page, 1981) contained measurable quantities of γ-HCH. Parts per trillion concentrations of γ-HCH have been detected in rain or snow samples from the Great Lakes (Canadian side)

(Strachan and Huneault, 1979), Portland, OR (Pankow et al., 1984), Canada (12 sites) (Brooksbank, 1983) and two sites in Lake Superior (Caribou Island and Isle Royale) (Strachan, 1985).

α-HCH has been detected at 2.7-20.3 and 0.45-9.7 ppt in municipal drinking water samples collected in the winter and summer, respectively, from 12 sites in Canada (Williams et al., 1982) and at 17 µg/ℓ in tap water collected in Ottawa, Ontario, Canada (Kraybill, 1977). An average daily intake of α-HCH of 0.90-40.6 ng was calculated (excluding the Ottawa result), assuming an average water consumption of 2 ℓ/day. Based on the high α-HCH content of tap water from Ontario, an average daily intake of 34 µg was estimated. The relatively high value of α-HCH in the Ottawa sample is thought to be nonrepresentative. Dissolved residues of α-HCH in water ranged from 0.019-0.14 µg/ℓ, with a mean concentration of 0.06025 µg/ℓ (U.S. EPA, 1985a). Surface water from Niagara-on-the-Lake (Kuntz and Warry, 1983), New Jersey (Page, 1981), Washington, DC and Denver, CO (Cole et al., 1984) contained measurable amounts of α-HCH. Parts per trillion concentrations have been detected in rain or snow samples from the Great Lakes (Canadian side) (Strachan and Huneault, 1979), the Great Lakes ecosystem (Eisenreich et al., 1981), Portland, OR (Pankow et al., 1984), Canada (12 sites) (Brooksbank, 1983) and two sites in Lake Superior (Caribou Island and Isle Royale) (Strachan, 1985).

The concentration of β-HCH ranged from 3-50 ng/ℓ, with a mean concentration of 17.75 ng/ℓ in three rivers; from 2-45 ng/ℓ, with a mean concentration of 13.3 ng/ℓ in freshwater regions of the Rotterdam; and from 1-40 ng/ℓ (no mean given) in estuarine regions in the Netherlands (Duinker and Hillebrand, 1979). Suspended and dissolved β-HCH ranged from 0-1.0 and 0.1-0.2 µg/ℓ, respectively. The mean concentrations were 0.75

and 0.1725 μg/ℓ, respectively (U.S. EPA, 1985a). Pertinent monitoring data for δ- or ε-HCH could not be located in the available literature as cited in the Appendix.

3.2. FOOD

A wide variety of foodstuffs, including meats, dairy products (except milk) and vegetables analyzed from 1971-1976, contained γ-HCH at ppb concentrations (Duggan et al., 1983). The average daily intake of γ-HCH based on these studies averaged over 1971-1976 is 0.27 g. Market basket surveys conducted in 1977-1978 revealed the presence of ppb concentrations in lunch meats, processed cheese, butter, frankfurters, pork chops, hamburger and round steak (Podrebarac, 1984). Based on these figures, the average daily intakes of γ-HCH in 1977 and 1978 were 3.8 and 2.4 ng/kg bw/day. Domestic fish samples were 0.7% positive for γ-HCH, with an average concentration of 0.2 ppb, and imported samples were 6.4% positive, with an average concentration of 1 ppb in samples taken from 1969-1976. Imported shellfish analyzed in the same time period contained a mean concentration of γ-HCH of 0.4 ppb in 2.7% of the samples (Duggan et al., 1983). The concentration of γ-HCH in a variety of fish collected across the United States contained <0.01-0.2 ppm γ-HCH (Schmitt et al., 1985). Residues of γ-HCH in 5026 dried samples of shellfish ranged from 5-100 ppb, with a mean of 7.703 ppm, and in 368 samples of shellfish, ranged from 0.001-44.0 ppb with a mean of 1.347 ppb (U.S. EPA, 1985a). Domestic samples of milk were 2.0% positive for γ-HCH, with a mean concentration of 2 ppb (Duggan et al., 1983).

Market basket surveys conducted in 1977-1978 indicated ppb concentrations of α-HCH in a variety of meats, cottage and processed cheese, ice cream, fish fillets and canned fish, lunch meat and frankfurters

(Podrebarac, 1984). Based on these figures, the average daily intakes of α-HCH in 1977 and 1978 were 10.5 and 9.1 ng/kg bw/day. The concentration of α-HCH in a variety of fish collected across the United States contained from <0.01-0.2 ppm α-HCH (Schmitt et al., 1985). Residues of α-HCH in 384 shellfish samples ranged from 0.005-63.0 ppm (wet weight), with a mean of 1.815 ppm (U.S. EPA, 1985a).

Residues of β-HCH in 375 shellfish samples ranged from 1.0-38.0 ppm (wet weight), with a mean concentration of 1.940 ppm, and δ-HCH ranged from 1.0-10.0 ppm, with a mean of 1.408 ppm in 375 shellfish samples (wet weight) (U.S. EPA, 1985a). Specific data for β-, δ- or ε-HCH were not located in the available literature. A variety of foodstuffs, including meats, dairy products (except milk) and vegetables analyzed from 1971-1976, contained ppb amounts of α-, β- and δ-HCH (combined residues) (Duggan et al., 1983). Based on these studies, the average daily intake of the combined α-, β- and δ-HCH residues is 0.67 g. The mean concentrations of combined α-, β- and δ-HCH isomers in 13.1% of domestic and 33.1% of imported fish samples were 48 and 1 ppb, respectively. The mean concentrations of the isomers in 8.1% of domestic and 22.6% of imported shellfish samples were 1 and 66 ppb, respectively (Duggan et al., 1983). In a 10-year study of chlorinated hydrocarbons in bovine milk in Illinois, the percent positive samples for all the isomers of HCH combined ranged from 68.6-91.8%, with average residues of 0.01-0.02 ppm. In 1980 and 1981, only 28.3-31% of the samples were positive, with average concentrations of trace (<0.001 ppm) to 0.01 ppm (Steffey et al., 1984). Mean concentrations of combined isomers of HCH in a variety of imported spices ranged from <0.005-0.51 ppm (Sullivan, 1980).

3.3. AIR

Monitoring during the years 1970-1972 revealed a mean concentration of γ-HCH in ambient air of 0.6 ng/m^3 for all years and all states combined. There were 67.7% positive samples with a mean concentration of 0.9 ng/m^3 and a maximum value of 11.7 ng/m^3 (Kutz et al., 1976). γ-HCH was also detected in measurable quantities in Jackson, MS; Fort Collins, CO (Kutz et al., 1976); Stoneville, MS (Arthur et al., 1976); Baltimore, MD; Iowa City, IA; Salt Lake City, UT (Stanley et al., 1971); and Miami, FL (Lewis and Lee, 1976). Assuming an average intake of 20 m^3 of air/day, the average daily intake of γ-HCH by inhalation is 18 ng, based on the monitoring data given above.

Monitoring during the years 1970-1972 revealed a mean α-HCH concentration in ambient air of 1.2 ng/m^3 in 87.37% of the samples for all states and years combined (Kutz et al., 1976). Measurable quantities of α-HCH were detected in the air of the Great Lakes ecosystem (Eisenreich et al., 1981); Baltimore, MD; Salt Lake City, UT, and Iowa City, IA (Stanley et al., 1971). Assuming a normal daily intake of 20 m^3 of air, the average daily intake of α-HCH, based on these monitoring data, is 24 ng. Pertinent monitoring data regarding the other isomers of HCH could not be located in the available literature as cited in the Appendix.

3.4. MISCELLANEOUS EXPOSURE

Transfer of unspecified amounts of α- and γ-HCH to smoke from pesticide-treated tobacco has been observed (Ceschini and Chauchaix, 1980); Rao-Kovvali et al. (1980) reported that Indian tobacco contains unspecified amounts of HCH isomers. Occupational exposure to q-HCH occurs in personnel operating commercial seed-treating equipment (Grey et al., 1983). The α-, β-, γ- and δ isomers of HCH have been detected at ppb concentrations in raw wastewater from coal mining, aluminum forming, foundries and nonferrous metals manufacturing (U.S. EPA, 1981). Raw wastewater from organic chemicals manufacturing/plastics industries contains ppb amounts of α-, γ- and δ-HCH. The γ- and δ- isomers were found in raw wastewater from metal finishing, and the δ- and β- isomers were found in paint and ink formulation and petroleum refining raw wastewater, all at ppb concentrations (U.S. EPA, 1981).

3.5. SUMMARY

γ-HCH concentrations of 0.01-0.319 ppb have been detected in drinking water from various rural and urban areas (Keith et al., 1976; Sandhu et al., 1978; Bevenue et al., 1972). Based on these figures and assuming an average daily consumption of 2 ℓ of water, an average daily γ-HCH intake of 0.02-0.638 μg was estimated. A γ-HCH concentration of 1.3 ppb was detected in Ottawa, Ontario (Kraybill, 1977). The average daily intake based on this figure is 2.6 μg, but this figure is considered to be nonrepresentative since the monitoring data on which it is based is so high relative to the other values. Surface water and precipitation (rain and snow) samples contained measurable concentrations of γ-HCH (U.S. EPA, 1985a; Oliver and Charlton, 1984; Cole et al., 1984; Saleh et al., 1982; Sandhu et al., 1978; Bevenue et al., 1972; Page, 1981; Strachan and Huneault, 1979; Pankow et al., 1984; Brooksbank, 1983; Strachan, 1985). α-HCH has been detected at 2.7-20.3 and 0.45-9.7 ppt municipal drinking water samples collected during the winter and summer, respectively (Williams et al., 1982) and at 17 μg/ℓ in tap water from Ottawa, Ontario (Kraybill, 1977). An average daily intake of α-HCH of 0.90-40.6 ng was estimated, assuming an average daily consumption of 2 ℓ of water (excluding the Ottawa result). Based on the high α-HCH content of the tap water from Ottawa, an average daily intake of 34 μg was estimated. Because of the relatively high value of α-HCH in the Ottawa sample, this value is thought to be nonrepresentative. Samples of surface water and precipitation (rain and snow) from a variety of locations contained α-HCH (U.S. EPA, 1985a; Kuntz and Warry, 1983; Page, 1981; Cole et al., 1984; Strachan and Huneault, 1979; Eisenreich et al., 1981; Pankow et al., 1984; Brooksbank, 1983; Strachan, 1985). In the Netherlands, β-HCH was found in ng quantities in a variety of locations (Duinker and Hillebrand, 1979). Samples of surface water in the United States contained a mean β-HCH concentration of 0.1725 μg/ℓ (U.S. EPA, 1985a). Pertinent monitoring data for δ- or ε-HCH could not be located in the available literature as cited in the Appendix.

A wide variety of foodstuffs, including dairy products, meat, vegetables, fruits and seafood, contain one or more HCH isomers (Duggan et al., 1983; Steffey et al., 1984; Podrebarac, 1984; Schmitt et al., 1985; U.S. EPA, 1985a). The average daily intake of γ-HCH was estimated to be 0.27 μg, based on the γ-HCH content in foods from 1971-1976, and that of α-HCH was estimated to be 10.5 and 9.1 ng/kg bw/day, based on 1977 and 1978 data, respectively. Since monitoring data in foods are available only for mixtures of the isomers, β-, δ- and ε-HCH, it is not possible to estimate the average daily intakes of individual isomers.

The mean concentration of γ-HCH in positive samples of ambient air in the United States in 1970-1972 was 0.9 ng/m^3 (Kutz et al., 1976). Based on this value and assuming an average intake of 20 m^3 air/day, the average daily intake of γ-HCH is 18 ng. Monitoring data during the years 1970-1972 revealed a mean α-HCH concentration in ambient air of 1.2 ng/m^3 in the positive samples collected across the United States (Kutz et al., 1976). Assuming an average daily intake of 20 m^3 of air, this figure is equivalent to an average daily intake of 24 ng. Pertinent monitoring data regarding the other isomers of HCH could not be located in the available literature as cited in the Appendix.

There are several miscellaneous sources of exposure to HCH isomers including burning of tobacco (Ceschini and Chauchaix, 1980) and the operation of commercial seed-treatment equipment (Grey et al., 1983). Isomers of HCH were detected in wastewater from coal mining, aluminum forming, foundries, nonferrous metals manufacturing, paint and ink formulation, petroleum refining, metal finishing and organic chemicals manufacturing/plastics industries (U.S. EPA, 1981).

4. PHARMACOKINETICS

4.1. ABSORPTION

Two studies provide direct evidence that γ-HCH is absorbed from the gastrointestinal tract. Turner and Shanks (1980) showed that 29.6-42.6% and 42.3-53.0% of 0.05 and 0.1 μmol of γ-HCH (dissolved in rat bile), respectively, were absorbed into the blood from injected intestinal loops of male Wistar rats. Ahdaya et al. (1981) administered radiolabeled γ-HCH (1 mg/kg in Emulphor:ethanol:water, 1:1:8) to fasted ICR mice by stomach needle and monitored the appearance of radioactivity in the gastrointestinal tract (minus contents), blood, liver and carcass and the disappearance of radioactivity from the gastrointestinal tract contents for up to 60 minutes after administration. Radioactivity in the gastrointestinal tract (minus contents) reached a maximum of 17% of the administered dose at ~8 minutes after treatment, then declined to 9% for the duration of the study. The amount of radioactivity in the blood reached a maximum of 2.2% of the administered dose within 15 minutes and then declined slightly (to ~1.5%) for the remainder of the study. Radioactivity in the liver reached a maximum of 8% within 15 minutes and declined to 5% by 60 minutes. By 60 minutes after treatment, 70.7% of the administered radioactivity was absorbed. The time for 50% absorption was estimated at 14.2±0.6 minutes, using an unspecified model that gave the best linearization.

In a study designed to investigate the possibility of isomerization, Eichler et al. (1983) administered either α-HCH (15 mg/kg/day) or γ-HCH (15 mg/kg/day males; 10 mg/kg/day females) by stomach tube to male and female rats for 56 days. The concentration of α-HCH peaked in the blood within 28 days of exposure (13-14 mg/kg blood) and remained at that level through 56 days of treatment. Peak levels of γ-HCH were also observed within 28 days of treatment (2.1 mg/kg blood), but then declined to 0.9 mg/kg blood by day 56 of treatment. Using methods with a detection limit of 0.001 mg/kg blood or tissue, Eichler et al. (1983) found no evidence of isomerization of α- or γ-HCH.

The appearance of β-HCH in the brain and adipose tissue of rats and minipigs after dietary administration of this isomer (11 weeks, rats; 37 weeks, minipigs) indicates that β-HCH is absorbed by the gastrointestinal tract (Altmann et al., 1983). No other details were given.

Muralidhara et al. (1979) demonstrated that the acute toxicity of γ-HCH is proportional to the solubility of γ-HCH in the carrier and suggested that poor solubility results in reduced absorption in the small intestine. Herbst and Bodenstein (1972) suggested that lipid-mediated carriers enhance the rapidity with which γ-HCH is absorbed.

4.2. DISTRIBUTION

In general, isomers of HCH tend to accumulate in fatty tissue. In a comparative study, Eichler et al. (1983) gavaged male and female rats with either α-HCH (15 mg/kg/day) or γ-HCH (15 mg/kg/day, males; 10 mg/kg/day, females after 15 days of 15 mg/kg/day) for 56 days. Both isomers were present in higher concentrations in the tissues studied (brain, liver, kidney and fat) than in the blood; levels in the fat were especially high. α-HCH accumulated in the fat and brain to a greater extent than did γ-HCH. Furthermore, the retention of α-HCH in the tissues was 10-20 times greater than that of γ-HCH. Tissue concentrations of γ-HCH decreased markedly during the 15 days after the termination of exposure. In contrast, concentrations of α-HCH remained high, particularly in the fat, even 15 days posttreatment. In other dietary and gavage studies in rats, isomers of HCH were shown to accumulate in fatty tissues (Chand and Ramachandran, 1980; Lakshmanan et al., 1979; Chadwick et al., 1978a; Altmann et al., 1983).

Chadwick et al. (1978a) and Lakshmanan et al. (1979) demonstrated that dietary factors can affect the retention of γ-HCH in the tissues. Chadwick et al. (1978a) found that rats fed a high-fiber diet for 28 days before dosing retained a significantly greater amount of radioactivity from ^{14}C-(γ-HCH) in the brain, liver, kidney, stomach and muscle than did rats fed a low-fiber diet. Retention was measured 24 hours after administration of a single oral dose of 2.87 mg ^{14}C-(γ-HCH). Lakshmanan et al. (1979) varied fat content in the diet of rats and found that rats maintained on a low-fat diet had significantly less γ-HCH in adipose tissue than did rats fed a high-fat diet. γ-HCH content of the brain was not affected by diet.

Human studies have shown that γ-HCH and other isomers of HCH accumulate in the fatty tissues (Baumann et al., 1980; Siddiqui et al., 1981a; Szymczynski and Waliszewski, 1981a). Investigators have also shown that γ-HCH accumulates in human milk and is able to cross the placenta (Siddiqui et al., 1981b; Poradovsky et al., 1977; Saxena et al., 1981; Welch and Findlay, 1981). Isomers of HCH (α, β, γ, δ and ε) have been detected in the semen of humans undergoing fertility analysis (Szymczynski and Waliszewski, 1981a,b). The α- and γ- isomers (but not β, δ or ε) were also found in testicular tissue. The concentration of HCH isomers in the semen (0.003 μg/g) and testes (0.009 μg/g) was considerably less than that found in fatty tissue (0.018 μg/g).

4.3. METABOLISM

The metabolism of HCH isomers primarily involves dehydrogenation, dehydrochlorination and dechlorination. Conjugation reactions with sulfuric and glucuronic acid and glutathione are also important (Macholz et al., 1982a; Engst et al., 1976, 1979; Chadwick et al., 1975; Grover and Sims, 1965; Freal and Chadwick, 1973; Chadwick and Freal, 1972; Allsup and Walsh, 1982; Kurihara et al., 1979). In mammals, including humans, common metabolites of HCHs include chlorinated phenols, chlorinated benzenes and pentachlorocyclohexenes (Angerer et al., 1983; Kujwa et al., 1977; Grover and Sims, 1965; Freal and Chadwick, 1973; Chadwick and Freal, 1972; Engst et al., 1976; Chadwick et al., 1975, 1978a). These metabolites are excreted in the urine and have also been identified in the blood, liver, kidney, spleen, heart and brain of rats fed γ-HCH (Engst et al., 1976).

Chadwick et al. (1975) demonstrated that in rats γ-HCH is metabolized to hexachlorocyclohexene, which is then degraded to 2,3,4,5,6-pentachloro-2-cyclohexene-1-ol, two tetrachlorophenols and three trichlorophenols. Macholz et al. (1982a) demonstrated that rats fed α-HCH in the diet for 30 days excreted all isomers of trichlorophenol and tetrachlorophenol in the urine. Similar results were obtained when rats were fed β-HCH in the same manner (Macholz et al., 1982b). Pentachlorocyclohexene was also identified as a metabolite of α-HCH but was not excreted in the urine.

A number of *in vitro* studies have shown that the metabolism of HCHs in mammals is probably mediated to a great extent by oxidative processes in hepatic microsomes (Gopalaswamy and Aiyar, 1984; Yamamoto et al., 1983; Fitzloff et al., 1982; Fitzloff and Pan, 1984; Baker et al., 1985; Tanaka et al., 1979; Portig et al., 1973).

Dietary factors have been shown to influence the metabolism and excretion of γ-HCH. Chadwick et al. (1978c) pretreated male Wistar rats with cadmium and then exposed them to ^{14}C-(γ-HCH). Cadmium-exposed rats excreted less radioactivity in the urine than did controls. Exposure to cadmium also inhibited the dehydrogenation of γ-HCH to hexachlorocyclohexene and altered the distribution of neutral to polar metabolites. Chadwick et al. (1978a) also demonstrated that rats fed high-fiber diets for 28 days before oral administration of γ-HCH, dehydrogenated and dechlorinated γ-HCH to a greater extent than did rats fed a low fiber diet.

Studies conducted by Liu (1982) suggested that metabolism of γ-HCH varies with the genetic strain of the animal studied. Long-term administration of γ-HCH resulted in lower levels of 2,4,6-trichlorophenol and 2,3,4,6-tetrachlorophenol in the blood of DBA/2 mice than in C57Bl/6 mice. Subsequently, however, levels of 2,3,4,6-tetrachlorophenol in DBA/2 mice exceeded those in C57Bl/6 mice. DBA/2 mice also had higher concentrations of 2,4,6-trichlorophenol in the liver, kidney and spleen.

4.4. EXCRETION

U.S. EPA (1980a, 1985a) concluded that even after prolonged administration, γ-HCH and its metabolites are completely excreted after application is terminated. Frawley and Fitzhugh (1949) demonstrated that γ-HCH concentration in the fatty tissue of rats dropped from 102 ppm to undetectable levels (sensitivity of method not reported) within 1 week after administration of γ-HCH was discontinued. Lehman (1952a,b) demonstrated a similar reduction (281 ppm to undetectable) within 2 weeks of discontinuation of exposure. Kitamura et al. (1970) observed that after 20 days of feeding γ-HCH at 10 ppm in the diet, no residues of γ-HCH could be detected in the bodies of rats within 1 day of return to the control diet. After 20 days of feeding α-HCH at 100 ppm in the diet, residues in the body declined to 0.1 ppm by 3 days after return to the control diet (Kitamura et al., 1970).

In a comparative study, Kitamura et al. (1970) demonstrated that the disappearance of γ-HCH from the bodies of mice given a single oral dose (500 μg) was more rapid than that of β-HCH under identical experimental conditions.

γ-HCH was eliminated more rapidly from fat than was α-HCH in a longer-term oral study (Eichler et al., 1983). In this study, γ-HCH levels in fat declined from a maximum of 385 to 15 ppm by 15 days after the termination of 56 days of oral administration of 10-15 mg/kg/day of γ-HCH to rats. In contrast, α-HCH accumulated to a maximum of 4255 ppm in fat and then declined to 1947 ppm by 15 days after the termination of 56 days of oral administration of 15 mg/kg/day of α-HCH to rats.

The principle route of excretion for γ-HCH and metabolites is urinary. When U-^{14}C-(γ-HCH) was administered orally to rats or intraperitoneally to mice, radioactivity was excreted primarily in the urine (Chadwick et al., 1978a; Engst et al., 1979). Following oral administration of U-^{14}C-[γ-HCH] to rats, lesser amounts of radioactivity appeared in the feces than in the urine (Chadwick et al., 1978a) and trace amounts (as $^{14}CO_2$) appeared in the expired air (Adhaya et al., 1981; Chadwick et al., 1978a).

Very little γ-HCH is excreted unaltered according to U.S. EPA (1980a, 1985a). Laug (1948) recovered only 4% of the administered dose of γ-HCH (not specified) as parent compound in the urine of rats fed γ-HCH. Egnst et al. (1976), however, reported that substantial amounts of free γ-HCH were excreted in the urine of rats administered 8 mg/kg/day of γ-HCH in sunflower oil by gavage for 19 days. Metabolites were also found in the urine. In the feces, only unaltered γ-HCH was detected. Excretion of urinary metabolites of γ-HCH, primarily in conjugated forms, has been reported by Kurihara et al. (1979), Chadwick et al. (1975, 1978a,b), Allsup and Walsh (1982), Zesch et al. (1982), Angerer et al. (1981) and Stein et al. (1980). Urinary excretion of α-HCH metabolites was reported by Macholz et al. (1982a).

In feeding studies, Chadwick et al. (1978a) demonstrated that dietary fiber can influence the metabolism and excretion of γ-HCH in rats given a single oral dose of 2.87 mg of U-^{14}C-(γ-HCH).

The feeding of high fiber diets (Purina Lab Chow or a low fiber diet supplemented with pectin) for 28 days before administration of γ-HCH was shown to cause significant increases in the excretion of radioactivity (as % of dose) in the urine (9.70-13.00% for high fiber diets vs. 7.85% for low fiber diet) and feces (3.55-4.12% for high fiber diets vs. 0.72% for low fiber diet) and significant increases in the amounts of conjugated chlorophenols and polar metabolites excreted in the urine.

Isomers of HCH are excreted in human milk (Herbst and Bodenstein, 1972; Welch and Findlay, 1981) and semen (Szymczynski and Waliszewski, 1981a,b). β-HCH accounts for 90% of the HCH found in human milk, while α- and γ-HCH accounts for the remaining 10%. All five isomers have been found in human semen.

4.5. SUMMARY

Two studies provide direct evidence that γ-HCH is absorbed from the gastrointestinal tract (Turner and Shanks, 1980; Ahdaya et al., 1981). The appearance of α-HCH and β-HCH in the blood and tissues after oral administration is also indicative of gastrointestinal absorption (Eichler et al., 1983; Altmann et al., 1983; Macholz et al., 1982a,b).

In general, isomers of HCH and their metabolites tend to accumulate in fatty tissue (Eichler et al., 1983; Chand and Ramachandran, 1980; Lakshmanan et al., 1979; Chadwick et al., 1978a; Altmann et al., 1983; Baumann et al., 1980; Siddiqui et al., 1981a; Szymczynski and Waliszewski, 1981a,b). In a comparative study where α-HCH or γ-HCH was fed to rats in the diet for 56 days, Eichler et al. (1983) found that α-HCH accumulated in the fat and brain to a greater extent than did γ-HCH. Furthermore, the retention of α-HCH in the tissues (fat, brain, liver, kidney) was 10-20 times greater than that of γ-HCH. Tissue concentrations of γ-HCH declined to a much greater extent than did tissue levels of α-HCH during the 15 days following termination of exposure.

The metabolism of HCH isomers primarily involves dehydrogenation, dehydrochlorination and dechlorination. Conjugation reactions with sulfuric and glucuronic acid are also important (Macholz et al., 1982a; Engst et al., 1976, 1979; Chadwick et al., 1975; Grover and Sims, 1965; Freal and Chadwick, 1973; Chadwick and Freal, 1972; Allsup and Walsh, 1982). In mammals, including humans, common metabolites of HCH include chlorinated phenols, chlorinated benzenes and pentachlorocyclohexenes. These metabolites are usually excreted in conjugated form (or a degradation product of a previously conjugated form) in the urine, and have also been detected in blood, liver, kidney, spleen, heart and brain (Engst et al., 1976; Chadwick et al., 1975, 1978a; Freal and Chadwick, 1973; Chadwick and Freal, 1972; Angerer et al., 1983; Kujwa et al., 1977; Grover and Sims, 1965). A number of in vitro studies have shown that the metabolism of HCHs in mammals is mediated to a great extent by oxidative processes in hepatic microsomes (Gopalaswamy and Aiyar, 1984; Yamamoto et al., 1983; Fitzloff et al., 1982; Fitzloff and Pan, 1984; Baker et al., 1985; Tanaka et al., 1979; Portig et al., 1973).

HCH isomers and metabolites have been recovered in the urine and feces (Ahdaya et al., 1981; Kurihara et al., 1979; Chadwick et al., 1975, 1978a,b; Allsup and Walsh, 1982; Zesch et al., 1982; Angerer et al., 1981; Stein et al., 1980; Macholz et al., 1982a,b), and trace amounts (as $^{14}CO_2$) have been detected in expired air (Ahdaya et al., 1981; Chadwick et al., 1978a). In comparative studies, Kitamura et al. (1970) and Eichler et al. (1983) demonstrated that the disappearance of γ-HCH from the bodies of mice given a single oral dose or rats given repeated oral doses was more rapid than that of β-HCH or α-HCH administered in the same manner. Isomers of HCH are known to be excreted in human milk (Herbst and Bodenstein, 1972; Welch and Findlay, 1981) and semen (Szymczynski and Waliszewski, 1981a,b).

Chadwick et al. (1978a,c) and Lakshmanan et al. (1979) have demonstrated that dietary factors (cadmium, fiber and fat) can alter the retention, metabolism and excretion of γ-HCH. Herbst and Bodenstein (1972) have suggested that lipid-mediated carriers enhance the absorption of γ-HCH. Liu (1982) suggested that the metabolism of γ-HCH might vary with the strain of animal used in the study.

5. EFFECTS

5.1. CARCINOGENICITY

5.1.1. α-HCH. Dietary α-HCH has been shown to cause increased incidences of liver tumors in five strains of mice (Ito et al., 1973a,b, 1976; Nagasaki et al., 1972a, 1975; Hanada et al., 1973; Goto et al., 1972) and in Wistar rats (Ito et al., 1975; Schulte-Hermann and Parzefall, 1981) (Table 5-1). None of the tests in mice were negative. However, the carcinogenicity in Wistar rats in these studies was either marginal or negative, indicating a greater sensitivity of the mouse to this compound.

Goto et al. (1972) reported that when control diet or diet containing 600 ppm of T-HCH, α-HCH, β-HCH, γ-HCH or a mixture of δ- and ε-HCH or 300 ppm γ-HCH was fed to ICR-JCL mice for 26 weeks, grossly observable hepatic nodules occurred in all mice fed T-HCH or α-HCH, in 5/10 mice fed γ-HCH and in 10/10 mice fed δ- and ε-HCH. By implication, no grossly observable hepatic nodules were seen in mice treated with 600 ppm β-HCH, 300 ppm γ-HCH or control diet. The report, written in German, indicates that histological examination revealed benign hepatomas in all groups treated with 600 ppm HCH as above and that malignant hepatomas were frequently found in the groups treated with α-HCH or δ- and ε-HCH. The report does not explicitly state the incidences of histologically confirmed benign or malignant hepatomas in any group.

5.1.2. β-HCH. Table 5-2 summarizes the available oral carcinogenicity studies on β-HCH. Dietary β-HCH has been shown to cause increased incidences of liver tumors only in CF1 mice with marginal increases in ICR-JCL mice (Thorpe and Walker, 1973; Goto et al., 1972) but no increased incidence in dd mice (Ito et al., 1973a,b; Hanada et al., 1973; Nagasaki et al., 1972a) or in Wistar rats (Ito et al., 1975; Fitzhugh et al., 1950).

TABLE 5-1

Summary of Oral Cancer Studies Conducted with α-HCH[a]

Species/Strain	No. and Sex/Group	Dose and Duration of Treatment	Response	Comments	Reference
Mice/DDY	12-21 M/group/ duration	0 or 500 ppm diet for 16, 20, 24 or 36 weeks; observation at intervals from 0-36 weeks after the end of exposure	+	No liver tumors in controls observed for 72 weeks (0/18) development of nodular hyperplasias and hepatocellular carcinoma in the livers of treated mice; incidence increased with duration of exposure and observation; 100% response observed after 24 weeks of treatment (20/20); histologically, most tumors were nodular hyperplasias up to 60-72 weeks of the study; after 60-72 weeks, most tumors were hepatocellular carcinomas; removal from diet promoted regression of some nodular hyperplasias but did not change incidences of hepatocellular carcinomas at $\geq$60 weeks	Ito et al., 1976
Mice/DDY, ICR, DBA/2, C3H/He, C57BL/6	13-29/sex/group	0 or 500 ppm diet for 24 weeks	+	Significantly increased incidence of hepatocellular carcinomas in male and female DDY and ICR mice; hepatocellular carcinomas were observed in one male and one female of DBA/2 strain and in none of the C3H/He or C57BL/6 mice; nodular hyperplasias were observed in all strains with the highest incidence in DDY mice (20/20 males, 16/20 females) and the lowest incidence in C57BL/6 mice (4/21 males, 3/18 females); no neoplasms were observed in controls	Nagasaki et al., 1975
Mice/DDY	20 M (exposed); 16 male controls	0 or 500 ppm diet for 24 weeks	+	No liver neoplasms in controls; all treated mice had nodular hyperplasia; 6/20 had hepatocellular carcinomas	Nagasaki et al., 1975
Mice/dd	20-30 M/group	0, 50, 100 or 250 ppm diet for 24 weeks	+	No liver neoplasms in controls or in mice fed 50 or 100 ppm; 23/30 fed 250 ppm had nodular hyperplasia; 8/30 had hepatocellular carcinoma	Ito et al., 1973b
Mice/dd	20-38 M/group	0, 100, 250 or 500 ppm diet for 24 weeks	+	No liver neoplasms were observed in controls or mice fed 100 ppm; of mice fed 250 ppm, 30/38 had liver neoplasms, 10/38 had hepatocellular carcinomas; all mice fed 500 ppm had liver neoplasms, 17/20 had hepatocellular carcinomas	Ito et al., 1973a
Mice/dd	21 M, 20 F controls (only 14 M, 15 F examined) 10-11/sex/treatment group (only 3-10/ sex/group examined)[b]	0, 100, 300 or 600 ppm for 32 weeks, followed by 5-6 weeks on control diet	+	No liver neoplasms in controls or females fed 100 ppm; 1/8 males fed 100 ppm had a hepatoma; 100% response (hepatomas) in males fed 300 or 600 ppm; 2/3 and 6/8 females fed 300 and 600 ppm, respectively, had hepatomas	Hanada et al., 1973

TABLE 5-1 (cont.)

Species/Strain	No. and Sex/Group	Dose and Duration of Treatment	Response	Comments	Reference
Mice/ICR/JCL	10 M/group examined; 20 M/group started on test[c]	0 or 600 ppm diet for 26 weeks	+	No liver neoplasms in controls; 10/10 exposed mice had grossly observable liver nodules; histological examination revealed benign and malignant hepatomas in exposed mice at unspecified incidences	Goto et al., 1972
Mice/dd	20 M/group	0, 100, 250 or 500 ppm for 24 weeks	+	0/20, 0/20, 9/20 and 20/20 mice fed 0, 100, 250 and 500 ppm, respectively, had grossly observable liver nodules; histologic examination of livers from 250 and 500 ppm groups revealed benign and malignant hepatomas at unspecified incidences	Nagasaki et al., 1972a
Rats/Wistar	10 M, 10 F/group (exposed) 20 M, 20 F controls	0, 10, 50, 100, 800 ppm diet for life	-	No increase in incidence of tumors, but not all rats were examined; 800 ppm significantly reduced lifespan (average lifespan = 35.9 weeks, 800 ppm vs. 58 weeks for controls	Fitzhugh et al., 1950
Rats/Wistar	5-16 males/group examined; 18-24 M/group started on test[d]	0, 500, 1000 or 1500 ppm diet for 24, 48 or 72 weeks	+	No liver neoplasms in eight controls examined after 72 weeks or in rats exposed to 500 ppm (24 or 48 weeks) or 1000 ppm for 24 weeks; neoplastic nodules were observed in 5/12, 12/16 and 10/13 rats fed 1000 ppm for 48 weeks, 1000 ppm for 72 weeks and 1500 ppm for 72 weeks, respectively; hepatocellular carcinomas were observed in 1/16 rats fed 1000 ppm for 72 weeks and in 3/13 rats fed 1500 ppm for 72 weeks (NOTE: rats that died during test were not examined).	Ito et al., 1975
Rats/Wistar	3-6 F/group examined	0 or ~20 mg/kg/day from the diet for 8-26 months	+	The incidence and severity of neoplastic lesions in the liver increased with duration of treatment; after 20-26 months of treatment, 5/6 rats fed α-HCH had neoplastic nodules and 1/6 had hepatocellular carcinoma; after 20-26 months, 1/6 controls had neoplastic nodules; hepatocellular carcinoma was not seen in controls	Schulte-Hermann and Parzefall, 1981

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[a] Detailed incidence data for positive studies are provided in Section 9.2.1.

[b] Only mice that survived ≥36 weeks were examined

[c] Study was still in progress at time of report according to IARC (1979)

[d] Rats dying during the experiment were not examined

TABLE 5-2

Summary of Oral Cancer Studies Conducted with β-HCH[a]

Species/Strain	No. and Sex/Group	Dose and Duration of Treatment	Response	Comments	Reference
Mice/dd	20 M/group	0, 100, 250 or 500 ppm diet for 24 weeks	-	No liver neoplasms were observed in any group	Ito et al., 1973a
Mice/dd	20 M/group	0, 50, 100 or 250 ppm diet for 24 weeks	-	No liver neoplasms were observed in any group	Ito et al., 1973b
Mice/dd	10-11/sex/treatment group started on test; 4-9/sex/group examined; 21 M, 20 F controls started on test; 14 M, 15 F examined[b]	0, 100, 300 or 600 ppm diet for 32 weeks, then control diet for 5-6 weeks	-	No liver neoplasms were observed in any group	Hanada et al., 1973
Mice/CFI	30 M, 30 F treated; 45 M, 44 F controls	0 or 200 ppm diet for 110 weeks	+	Increased incidences of liver neoplasms (benign and malignant) were observed in exposed male (92% vs. 24% controls) and female (68% vs. 23% control) mice; lung metastases were observed in 4/30 exposed males but not in any other group	Thorpe and Walker, 1973
Mice/ICR-JCL	10 M/group examined; 20 M/group started on test[c]	0 or 600 ppm for 26 weeks	- +	No liver neoplasms in controls; exposed mice had grossly observable liver nodules; histological examination revealed benign hepatomas in exposed mice but incidence is unclear (see Section 5.1.1.)	Goto et al., 1972
Mice/dd	20 M/group	0, 100, 250 or 500 ppm for 24 weeks	-	No grossly observable liver nodules were observed in any group	Nagasaki et al., 1972a
Rats/Wistar	18-24 M/group started on test; 5-8/group examined[d]	0, 500, 1000 ppm diet for 24, 48 or 72 weeks	-	No liver neoplasms were observed in any group	Ito et al., 1975
Rats/Wistar	10 M, 10 F/group; 20 M, 20 F controls	0, 10, 100, 800 ppm diet for life	-	No increase in tumors of any type were observed in any group, but high dose rats survived only for an average of 4.4 weeks; not all animals were examined histologically	Fitzhugh et al., 1950

[a] Detailed incidence data for positive study (Thorpe and Walker, 1973) are provided in Section 9.2.2.

[b] Only mice that survived ≥36 weeks were examined

[c] Study was still in progress at time of report according to IARC (1979)

[d] Rats dying during the experiment were not examined

The studies with negative results, however, were of short duration (Hanada et al., 1973; Ito et al., 1973a,b; Nagasaki et al., 1972a), used small numbers of animals [except Thorpe and Walker (1973)], or failed to examine all the experimental animals (Fitzhugh et al., 1950; Nagasaki et al., 1972a; Hanada et al., 1973). These studies that were observed to be negative for β-HCH might have been expected to yield negative results because of study design limitations and, therefore, are only of limited utility.

5.1.3. γ-HCH. Dietary γ-HCH was shown in one study to cause an increased incidence of liver tumors in male CF1 mice fed 400 ppm for 110 weeks (Thorpe and Walker, 1973). Marginal results were observed in male ICR-JCL mice fed 600 ppm for 26 weeks (Goto et al., 1972). The Thorpe and Walker (1973) study was the only full-term study in mice since the other studies in mice were terminated at shorter than lifetime testing durations (24, 24, 32, 26 and 24 weeks). Only the most potent carcinogens would display clear results in these shorter duration studies. For example, no liver tumors were observed in dd mice fed up to 500 ppm for 24 weeks (Ito et al., 1973a,b; Nagasaki et al., 1972a) or in Wistar rats fed 500 ppm for up to 48 weeks (Ito et al., 1975). Significant compound-related development of tumors of any type was not observed in NMRI mice (Herbst et al., 1975; Weisse and Herbst, 1977), B6C3F1 mice (NCI, 1977) Osborne-Mendel rats (NCI, 1977) or Wistar rats (Fitzhugh et al., 1950). The rat study conducted by NCI (1977) has been criticized for poor survival, changes in dosing regime and the possibility that male rats did not receive MTDs (IARC, 1979). Reuber (1979) also disputed the negative findings of NCI (1977) and reported that an independent interpretation of the histological data leads to the conclusion that γ-HCH is carcinogenic in both rats and mice. The validity of this assessment is uncertain. The negative findings of Fitzhugh et al.

(1950), Ito et al. (1973a,b, 1975) and Nagasaki et al. (1972a) are attributed in part to small numbers of animals, short duration or failure to examine all animals in the study. Table 5-3 summarizes these oral carcinogenicity studies. A metabolite of γ-HCH, 2,4,6-trichlorophenol, is carcinogenic in rats and mice and has been classified as a "probable" human carcinogen (Group B2). This metabolite has been identified in rodents and humans.

5.1.4. δ-HCH. Oral carcinogenicity data for δ-HCH are presented in Table 5-4. Dietary δ-HCH did not cause neoplastic or nonneoplastic changes in the livers of male dd mice (Ito et al., 1973a; Nagasaki et al., 1972a) or male Wistar rats (Ito et al., 1975). However, these negative studies are of limited utility. These studies used small numbers of animals and were only conducted for 24 weeks. Furthermore, Nagasaki et al. (1972a) failed to examine all the mice started on the test.

Goto et al. (1972) reported that a mixture of δ-HCH and ε-HCH caused increased incidences of benign and malignant hepatomas in ICR-JCL mice after 26 weeks of dietary administration, but the individual isomers were not tested in the study (see Section 5.1.1.).

5.1.5. ε-HCH. No direct cancer data exist for ε-HCH. Goto et al. (1972) reported that a mixture of δ-HCH and ε-HCH caused an increased incidence of benign and malignant hepatomas in ICR-JCL mice after 26 weeks of dietary administration, but the individual isomers were not tested in the study (see Section 5.1.1.). Additional pertinent data regarding the carcinogenicity of ε-HCH could not be located in the available literature as cited in the Appendix.

5.1.6. T-HCH. The T-HCH mixture has been shown to cause increased incidences of liver neoplasms in four strains of mice (Hanada et al., 1973; Goto et al., 1972; Kashyap et al., 1979; Nigam et al., 1984a; Bhatt et al.,

TABLE 5-3

Summary of Oral Cancer Studies Conducted with γ-HCH (Lindane)[a]

Species/Strain	No. and Sex/Group	Dose and Duration of Treatment	Response	Comments	Reference
Mice/dd	20 M/group	0, 100, 250, 500 ppm diet for 24 weeks	-	No liver tumors were observed in any group	Ito et al., 1973a
Mice/dd	20-28 M/group	0, 50, 100, 250 ppm diet for 24 weeks	-	No liver tumors were observed in any group	Ito et al., 1973b
Mice/dd	10-11/sex/treatment group started on test; 3-10/sex/group examined; 21 M, 20 F controls started on test; 14 M, 15 F examined[b]	0, 100, 300, 600 ppm diet for 32 weeks, then control diet for 5-6 weeks	±	No liver tumors were observed in controls or mice fed up to 300 ppm; hepatomas were found in 3/4 males and 1/3 females fed 600 ppm	Hanada et al., 1973
Mice/dd	20 M/group	0, 100, 250, 500 ppm diet for 24 weeks	-	No grossly observable liver nodules were observed in any group	Nagasaki et al., 1972a
Mice/CF1	29 M, 29 F exposed; 45 M, 44 F controls	0, 400 ppm diet for 110 weeks	+	11/45 (24%) male and 10/44 (23%) female controls had liver tumors; 27/28 (96%) male and 20/21 (95%) treated female mice had liver tumors; 3/29 males and 9/29 treated females had lung metastases	Thorpe and Walker, 1973
Mice/ICR-JCL	10 M/group examined; 20 M/group started on test[c]	0, 300, 600 ppm diet for 26 weeks	±	No liver neoplasms in controls or 300 ppm group; 5/10 mice fed 600 ppm had grossly observable liver nodules; histological examination revealed benign hepatomas in 600 ppm group but incidence is unclear (see Section 5.1.1.)	Goto et al., 1972
Mice/NMRI	50 M, 50 F/treatment group; 100 M, 100 F controls	0, 12.5, 25 or 50 ppm diet for 80 weeks	-	No treatment-related effects on mortality or development of tumors; liver and lung tumors, lymphosarcomas and lymphocytic leukemia were observed	Herbst et al., 1975; Weisse and Herbst, 1977
Mice/B6C3F1	50 M, 50 F/treatment group; 10 M, 10 F matched controls; 40 M, 40 F pooled controls	0, 80 or 160 ppm for 80 weeks, then control diet for 10-11 weeks	- +	No compound-related increase in the incidence of tumors; a significant increase in the incidence of hepatocellular carcinoma was observed only when low dose males were compared with pooled controls (19/49, 5/49, 2/10, 75/360 for low dose males, pooled controls, matched controls, and historical controls, respectively)	NCI, 1977

TABLE 5-3 (cont.)

Species/Strain	No. and Sex/Group	Dose and Duration of Treatment	Response	Comments	Reference
Rats/Osborne-Mendel	50 M, 50 F/treatment group; 10 M, 10 F matched controls 45 M, 45 F pooled controls	males: 320 or 640 ppm for 38 weeks, then 160 or 320 ppm for 42 weeks (TWA = 236 or 472 ppm) females: 320 or 640 ppm for 2 weeks, then 160 or 320 ppm for 47 weeks then 80 or 160 ppm for 31 weeks (TWA = 135 or 270 ppm). Both males and females were fed the control diet for an additional 29-30 weeks after treatment.	-	No statistically-significant, compound-related tumors were observed; IARC (1979) criticized this study for poor survival, small number of matched controls and because males probably did not receive the MTD.	NCI, 1977
Rats/Wistar	18-24 M/group started on test; only 6-8/group examined[d]	0, 500 ppm diet for 24 or 48 weeks	-	No liver tumors were observed in any group	Ito et al., 1975
Rats/Wistar	20 M, 20 F controls; 10 M, 10 F/treatment group	0, 5, 10, 50, 100, 400, 800 or 1600 ppm diet in corn oil for life or 0, 10, 100 or 800 ppm diet in powdered form for life	-	No compound-related increase in tumors of any type; significant reduction in lifespan in rats fed 800 or 1600 ppm in corn oil, but not at any dose in powdered form (Note: only small numbers of rats were examined microscopically)	Fitzhugh et al., 1950

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[a] Detailed incidence data for positive studies are provided in Section 9.2.3.

[b] Only mice that survived ≥ 36 weeks were examined

[c] Study was still in progress at time of report according to IARC (1979)

[d] Rats dying during the experiment were not examined

TABLE 5-4

Summary of Oral Cancer Studies Conducted with δ-HCH

Species/ Strain	No. and Sex/Group	Dose and Duration of Treatment	Response	Comments	Reference
Mice/dd	20 M/group	0, 100, 250 or 500 ppm diet for 24 weeks	-	No liver tumors were observed in any group	Ito et al., 1973a; Nagasaki et al., 1972a
Rats/Wistar	18-24 M/group started on test; only 6-8/group examined*	0, 500 or 1000 ppm diet for 24 or 48 weeks	-	No liver tumors were observed in any group	Ito et al., 1975

*Rats dying during the experiment were not examined

1981; Munir et al., 1983; Nagasaki et al., 1971, 1972b; Nagasaki, 1973; Munir and Bhide, 1984). However, carcinogenicity was not observed in Wistar rats (Munir et al., 1983) nor in Syrian Golden hamsters (Munir et al., 1983) (Table 5-5).

5.1.7. General Comments. All but six of the carcinogenicity studies [Fitzhugh et al., 1950 (α, β, γ); Herbst et al., 1975 (γ); Weisse and Herbst, 1977 (γ); Ito et al., 1975 (α, β, γ, δ); NCI, 1977 (γ); Thorpe and Walker, 1973 (β, γ)] assayed only for hepatic response, i.e., a full examination of other tissues was not done. A large body of evidence indicates that the nonneoplastic changes in the liver associated with exposure to isomers of HCH or T-HCH are associated with neoplastic development. A clear progression of hepatic changes, which ultimately leads to the development of malignant tumors has been observed at gross, histological and ultrastructural levels of examination; these changes, proportional to dose and duration of treatment, are reversible only at the very earliest stages before the development of nodular hyperplasia. The transition from reversible to irreversible change has not been accurately defined, but is characteristic of tumor progression which has been widely reported (Ito et al., 1975, 1976; Schulte-Hermann and Parzefall, 1981; Munir et al., 1983; Munir and Bhide, 1984; Nigam et al., 1982, 1984a; Sugihara et al., 1975).

5.2. MUTAGENICITY

γ-HCH was not found to be mutagenic in Ames tests on Salmonella typhimurium with or without S-9 (Lawlor et al., 1979; Probst et al., 1981) or Escherichia coli (Probst et al., 1981). Negative results with γ-HCH were also obtained in an oral dominant lethal test on SPF:THOM rats (Rohrborn, 1977), in an intraperitoneal dominant lethal test on mice (U.S. EPA, 1973) and in a recessive lethal test on Drosophila melanogaster (Benes and Sram,

TABLE 5-5

Summary of Oral Cancer Studies Conducted with T-HCH^a
(T-HCH is typically 65% α, 7% β, 17% γ, 4% ε and 10% other isomers)

Species/Strain	No. and Sex/Group	Dose and Duration of Treatment	Response	Comments	Reference
Mice/dd	10-11/sex/treatment started on test; 4-10/sex/treatment examined; 21 M, 20 F controls started on test; 14 M, 15 F examined^b	0, 100, 300 or 600 ppm diet for 32 weeks, then control diet for 5-6 weeks	-	No liver tumors in controls or mice fed 100 ppm; hepatomas were observed in 4/4 males and 3/5 females fed 300 ppm and in 4/4 males and 5/5 females fed 600 ppm	Hanada et al., 1973
Mice/dd	20 M/exposed group 14 M controls	6.6, 66 or 660 ppm diet for 24 weeks	+	20/20 mice fed 660 ppm developed hepatomas; no liver tumors in any other group	Nagasaki et al., 1971, 1972b; Nagasaki, 1973
Mice/ICR-JCL	10 M/group examined; 20 M/group started on test^c	0 or 600 ppm diet for 26 weeks	±	No liver neoplasms in controls; 10/10 exposed mice had grossly observable liver nodules; histological examination revealed benign hepatomas in exposed mice but incidences are unclear (see Section 5.1.2.)	Goto et al., 1972
Mice/Swiss	30/sex/group	0, 10 mg/kg/day (olive oil) or 100 ppm diet for 80 weeks	+	Increased incidence of animals with liver tumors and in total numbers of animals with tumors among all treated mice	Kashyap et al., 1979
Mice/Swiss	6-15 M/treatment; 75 controls	500 ppm diet for 2, 4, 6 or 8 months, followed by control diet for either 4 or 10 months	+	Increased incidence and severity of liver neoplasms proportional to duration of treatment and observation; no liver tumors in mice fed 500 ppm for 2 months and observed up to 10 months; neoplastic nodules observed in 6/15 after 4 months of treatment plus 10 months observation; appearance of hepatocellular carcinoma and pulmonary metastases after 6 months of treatment	Nigam et al., 1984a
Mice/Swiss	5/NR/group	0 or 500 ppm diet for 2, 4 or 6 or 8 months, followed by control diet for either 4 or 10 months	±	Appearance of neoplastic nodules after 4 months of treatment; incidences were not reported	Bhatt et al., 1981
Mice/Swiss	NR/M	0 or 500 ppm for 3, 7 or 10 months	+	Progression of changes; development of centrilobular necrosis (3 months), benign nodules or adenomas (7 months) and hepatocellular carcinoma ("almost all animals" after 10 months); exact incidences not reported.	Munir and Bhide, 1984

TABLE 5-5 (cont.)

Species/Strain	No. and Sex/Group	Dose and Duration of Treatment	Response	Comments	Reference
Mice/Swiss	10-37 M/group	0, 125, 250 or 500 ppm from 8-10 weeks of age to 8-11, 12-14, 15-17 or 18-22 months of age	+	Dose and duration-related increase in liver neoplasms for the four age groups; incidences were: 125 ppm -- 0/10, 0/10, 8/20 and 9/15; 250 ppm -- 4/17, 9/12, 12/12 and not measured; 500 ppm -- 28/37, 10/10, not measured and not measured	Munir et al., 1983
Mice/Swiss and BALB/C	10-37/sex/group	0 or 500 ppm from 8-10 weeks of age for 6-8, 8-10, 10-12 or 15-20 months	+	Incidence and severity of liver tumors increased with age and duration of treatment; for Swiss mice, 100% response was observed at 12-14 months of age in males (10/10 vs. 0/16 control), and at 15-20 months of age in both males and females (14/14 vs. 1/20 controls); 100% response was observed in BALB/c mice at 12-14 months (10/10 vs. 0/8 controls, males; 10/10 vs. 0/9 controls, females)	Munir et al., 1983
Rats/Wistar	≥10/sex/group	0 or 500 ppm diet until moribund	-	70% survived 2.5 years; no liver tumors	Munir et al., 1983
Hamsters/ Syrian golden	≥10/sex/group	0 or 500 ppm diet until moribund	-	70% survived 2.5 years; no liver tumors	Munir et al., 1983

[a] Detailed incidence data for positive studies are provided in Section 9.2.6.

[b] Only mice that survived ≥36 weeks were examined

[c] Study was still in progress at time of report according to IARC (1979)

[d] Rats dying during the experiment were not examined

NR = Not reported

1969). Rohrborn (1977) reported that weakly mutagenic effects were caused by γ-HCH in a host-mediated assay with S. typhimurium, while Buselmaier et al. (1972) reported negative results for γ-HCH in host-mediated assays with S. typhimurium and Serratia narcescens. Tests of γ-HCH-induced genotoxicity have yielded both positive and negative results. Chinese hamster fibroblasts (Ishidate and Odashima, 1977) and human peripheral lymphocytes (Tzoneva-Maneva et al., 1971). In contrast, γ-HCH did not cause chromosomal aberrations in lymphocytes of lindane production workers (Kiraly et al., 1979) or in bone marrow from Chinese hamsters (Rohrborn, 1977), did not cause unscheduled DNA synthesis in SV-40 transformed human fibroblasts (Ahmed et al., 1977) or human lymphocytes (Rocchi et al., 1980), did not increase micronucleus formation in epithelial cells from C3H mice (DeBrabander et al., 1976) or CBA mice (Jenssen and Ramel, 1980), and failed to induce DNA repair in primary cultures of rat hepatocytes (Probst et al., 1981).

α-HCH was not mutagenic with or without S-9 in reversion assays with Saccharomyces cerevisiae (Shahin and Von Borstel, 1977) or E. coli (Moriya et al., 1983), but caused increased mitotic activity in A. cepa roots (Nybom and Knutsson, 1947) and in hepatic parenchymal cells of rats fed 0.06% in the diet for 3 weeks (Hitachi et al., 1975).

Shimazu et al. (1976) reported that β-HCH caused chromosomal aberrations in bone marrow cells taken from LE rats injected i.p. with 0.01-10 mM/kg bw β-HCH. Which dose levels were considered positive were not reported.

T-HCH did not promote mutation in an Ames test with S. typhimurium (Anderson and Styles, 1978), but yielded positive results in a dominant lethal test where Swiss mice were fed 500 ppm for 4, 6 or 8 months (Lakkad et al., 1982). Furthermore, Babu et al. (1981) reported that prolonged dietary exposure (5-8 months) but not after 3 months to 500 ppm T-HCH inhibited meiotic division in the testes but not mitotic division in the bone marrow of Swiss mice. Bone marrow metaphases did not indicate an increase in chromosome aberrations.

A mixture of α-, β- and γ-HCH was not mutagenic in a rec assay with *Bacillus subtilis* or in reversion assays with *E. coli* or *S. typhimurium* (Shirasu et al., 1976). γ-HCH has been shown to cause mitotic arrest at metaphase in *Allium cepa* (Nybom and Knutsson, 1947) and *Pisum sativum* (Baquar and Khan, 1971; Sharma and Gosh, 1969), and caused chromosome aberrations in *A. cepa* roots (Sax and Sax, 1968). Additional information for the above studies is given in Table 5-6.

5.3. TERATOGENICITY

A majority of the studies available suggest that γ-HCH is not teratogenic.

Khera et al. (1979) administered 0, 6.25, 12.5 or 25 mg γ-HCH/kg bw by gavage (vehicle = corn oil) to groups of 20 female Wistar rats on days 6-15 of gestation. On day 22 of gestation, there were no differences between control and γ-HCH-treated rats in terms of numbers of pregnancies, abortions, corpora lutea/pregnancy, live fetuses/pregnancy, dead or resorbed fetuses, anomalous fetuses/number examined or litters with anomalous fetuses/number of litters examined. Furthermore, there were no compound-related effects on fetal body weight.

Palmer et al. (1978a) conducted a 3-generation reproduction study on CD rats. Groups of 10 male and 20 female weanling rats were fed 0, 25, 50 or 100 ppm γ-HCH in the diet for 60 days before mating, and were then mated to produce two litters. A similar protocol was used for the F_1 and F_2 generations. Mating performance, pup mortality, number of viable offspring

TABLE 5-6

Summary of Mutagenicity Data

Compound	Test System	Exposure/Dose	Response	Reference
α, β and γ-Hexachlorocyclohexane, % NS	*B. subtillus* rec assay strains H17 Rec^+ and H45 Rec^-	1 mg/mℓ, 0.02 mℓ	-	Shirasu et al., 1976
	E. coli WP2 plate assay	1 mg/mℓ, 0.02 mℓ	-	Shirasu et al., 1976
	S. typhimurium TA1535, TA1536, TA1537, TA1538	1 mg/mℓ, 0.02 mℓ	-	Shirasu et al., 1976
α-Hexachlorocyclohexane purity NS	*S. cerevisiae* XV185-14C	10-20 μg/mℓ	-	Shahin and Von Barstel, 1977
Lindane, purity NS	*S. typhimurium* TA98, TA100, TA1535, TA1537 ± S-9	5 dose levels NS	-	Lawlor et al., 1979
Hexachlorocyclohexane isomers NS	*S. typhimurium* TA100, TA1535, TA1538 + S-9	dose levels NS 10,000-fold range	-	Purchase et al., 1978
Lindane, purity NS	*S. typhimurium* TA1000, TA1535, TA1537, TA1538, TA98, C3076, D3052, G46	NS	-	Probst et al., 1981
	E. coli WP2, WP2 uvr A^-	NS	-	Probst et al., 1981

TABLE 5-6 (cont.)

Compound	Test System	Exposure/Dose	Response	Reference
Lindane, purity NS	Host-mediated assay Host: male NMRI mice given 0.5, 5, 50 mg/kg. Indicator: *S. typhimurium* TA1535	NS	+ at highest host exposure	Rohrborn, 1977
Technical HCH	Dominant lethal, Swiss mice	500 ppm in diet for 4, 6 or 8 months	significant increases in dead implants and embryos	Lakkad et al., 1982
Lindane, purity NS	Dominent lethal, mice	i.p. injection, 12.5, 25, 50 mg/kg	-	U.S. EPA, 1973
	Dominant lethal, rats	gavage, up to 15 mg/kg	-	Rohrborn, 1977
	Drosophila sex-linked, recessive mutations	0.001% in saline, 2 µℓ/animal	-	Benes and Sram, 1969
	Chinese hamster fibroblasts (CHL) chromatid abnormalities	0.63-2.1 mg/mℓ	± "suspicious" did not meet criteria for positive	Ishidate and Odashima, 1977
	Rat hepatocyte UDS	concentration NS	-	Probst et al., 1981

TABLE 5-6 (cont.)

Compound	Test System	Exposure/Dose	Response	Reference
Lindane, purity NS	Evaluation of chromosome abberations in lymphocytes of lindane workers	workers employed a minimum of 6 months	-	Kiraly et al., 1979
Lindane, 99.5%	Human lymphocyte UDS	500 µg/mℓ	- for UDS, + for suppression of scheduled synthesis and suppression of repair following UV irradiation; no statistical analysis	Rocchi et al.,
Lindane, purity NS	UDS in human fibroblasts (VA-4) with and without S-9	1, 1000 µM	-	Ahmed et al., 1977
HCH, technical	male Swiss mice, bone marrow evaluations for chromosomal abnormalities	500 ppm in diet for 8 months	-	Babu et al., 1981
Lindane, purity NS	micronucleus test, CBA male mice	75 mg/kg i.p. injection	-	Jenssen and Ramel, 1980
1,2,3,4,5,6-HCH, purity NS	*S. typhimurium* TA100, TA98, TA1535, TA1537, TA1538; *E. coli* WP2 hcr	up to 500 µg/plate	-	Moriya et al., 1983
HCH, purity NS	*S. typhimurium* TA1538, TA98, ± S-9	5 doses ranging from 4-2500 µg/plate	-	Anderson and Styles, 1978

NS = Not stated

and examination for external and internal malformations (at 21 days of age) was conducted for all generations. Ten males and 10 females in each group of the F_{3b} generation were examined for skeletal defects; organ weights were measured on an additional 10 pups/sex/group, and histological examination of major organs was conducted on 10 pups/sex from the high-dose groups. There were no compound-related effects on reproduction and no compound-related teratogenic effects in any generation. A dose-related increase in liver weight was observed, and enlarged hepatocytes were observed in some controls and treated males and females of the F_{3b} generation. Palmer et al. (1978a) considered the latter findings to be of doubtful importance when compared with the lack of effects on growth and reproductive performance.

Palmer et al. (1978b) did not observe compound-related teratogenic effects in CFY rats gavaged with 0, 5, 10 or 15 mg γ-HCH/kg on days 6-16 of gestation, or in New Zealand White rabbits gavaged similarly on days 6-18 of gestation.

In an effort to screen compounds to recommend for teratology testing, Chernoff and Kavlock (1983) and Gray and Kavlock (1984) monitored the growth and viability of progeny from CD-1 mice gavaged with 25 mg γ-HCH/kg on days 8-12 of gestation. There were no effects on incidence of pregnant females (~25/group tested), maternal mortality or body weight. There were no significant compound-related effects on the growth and viability of progeny observed for up to 250 days.

In contrast to the negative findings, Dzierzawski (1977) reported a 2- to 20-fold increase in the number of resorbed fetuses in hamsters given (route not specified) 40 mg γ-HCH/kg on day 8 of gestation, in rabbits given 40 or 60 mg γ-HCH/kg on day 9 of gestation, in rats given 50 or 100 mg γ-HCH/kg on day 9 of gestation and in rats given 40 mg γ-HCH/kg on days 6, 8 and 10 of gestation.

Pertinent data regarding the teratogenicity of other isomers of HCH could not be located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Palmer et al. (1978a) failed to observe adverse effects on reproduction in three generations of CD rats fed up to 100 ppm γ-HCH in the diet (see Section 5.3.). In contrast, Shtenberg and Mametkuliev (1976) reported that rats exposed orally to 5 mg/kg/day γ-HCH for 5 months had reduced mating and pregnancy indices, regardless of whether females were mated to treated or control males. Administration of 0.05 mg/kg for 9 months had no adverse effects on the gonads. Other details, such as whether 5 mg/kg and 0.05 mg/kg represent dietary concentrations or actual doses were not reported. Other studies suggest that low doses of γ-HCH given to rats and rabbits for several generations causes adverse effects on reproduction and on the developing fetus (Khamidov, 1984; Petescu et al., 1974); however, these studies were available only as abstracts and details were limited.

Saxena et al. (1980) and Wassermann et al. (1982) studied the possible association between body levels of organochlorine pesticides and premature labor in humans. Although premature labor was correlated with increased levels of γ-HCH in the blood, other organochlorine pesticides were also present at elevated concentrations.

Pertinent data regarding other reproductive effects of other isomers of HCH could not be located in the available literature as cited in the Appendix.

5.4.1. Testicular Effects. Testicular atrophy has been observed in rats and mice fed T-HCH and in rats gavaged with γ-HCH. In general, the atrophy was characterized by degenerative changes in the seminiferous epithelium, reduction in number of spermatocytes and the appearance of multinucleated giant cells.

Shivanandappa and Krishnakumari (1981, 1983) fed 0, 100, 750 and 1500 ppm T-HCH (equivalent to 0, 80, 625 and 1174 mg/rat/90 days) to groups of 10 weanling male Wistar rats for 90 days. Significant effects including mortality (two deaths at 8 weeks), reductions in body weight and food consumption (7-13 weeks), decreases in testicular weight, seminiferous tubule diameter, Leydig cell diameter and testicular enzyme activities, and increases in total lipid and total cholesterol content of the testes were observed only among rats fed 1500 ppm T-HCH.

Nigam et al. (1979) fed 0 or 500 ppm T-HCH to male Swiss mice for up to 10 months. Groups of six mice were killed each month and the testes were weighed and examined histologically. Mice exposed to T-HCH had histological evidence of testicular atrophy and increased testicular weight at $\geq$3 months of treatment. This study provided few details.

Dikshith and Datta (1977) and Dikshith et al. (1978) reported testicular atrophy in adult ITRC rats gavaged with 17.6 mg γ-HCH/kg bw (in peanut oil) for 90 days.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

5.5.1. α-HCH. The available chronic and subchronic oral studies on α-HCH are summarized in Table 5-7. Five of these studies were designed primarily to investigate and characterize the hepatic carcinogenic response (Schulte-Hermann and Parzefall, 1981; Ito et al., 1973a,b, 1975, 1976). In these studies, nonneoplastic hepatic changes (increased liver weight, cellular hypertrophy, bile duct proliferation and changes in activities of drug metabolizing enzymes) were observed only in rats and mice exposed to concentrations of α-HCH that also produced tumors. Furthermore, these studies used small numbers of animals, and in some cases (Ito et al., 1973a,b), were conducted for relatively short durations.

TABLE 5-7

Oral Toxicity Summary for α-HCH

Species/ Strain	No. and Sex/Group	Dose and Duration of Treatment	Endpoints Monitored	Effects	Reference
Rat/Wistar	10/sex/group exposed; 20/sex, controls	0, 10, 50, 100 or 800 ppm diet for life	growth, food consumption, mortality, organ weights, gross pathology; microscopic pathology was conducted only on 8-15 animals/treatment	Significantly reduced survival (800 ppm); significant reduction in growth rats (800 ppm); significantly increased relative liver weight (50-800 ppm); gross and microscopic evidence of moderate liver damage (800 ppm); microscopic evidence of slight to moderate kidney damage; no evidence of compound-related tumors	Fitzhugh et al., 1950
Rat/Wistar	1-8 F/group	0 or 20 mg/kg/day in the diet for ~4.5 months, 1 and 2 years	growth, food consumption, liver weight, liver protein, RNA and DNA, hepatic drug metabolizing enzymes, gross and microscopic evaluation of the liver	Significantly reduced final body weight; significantly increased liver weight, protein, RNA and DNA contents at all time-points; significantly increased activities (all time-points) of cytochrome P-450, monoxygenases, glutathione transferase and 3 N-demethylases; increased cytochrome P-450 content; by 20-26 months, all treated and control rats had microscopically-defined lesions, controls had only foci of altered cells, while treated rats had neoplastic nodules (5/6) and hepatocellular carcinoma (1/6)	Schulte-Hermann and Parzefall, 1981
Rat/Wistar	18-24 M/group started on test; 5-16/group examined	0, 500, 1000 or 1500 ppm diet for 24, 48 or 72 weeks	growth, gross and histological examination of tissues with emphasis on the liver	Slight to moderate nonneoplastic changes in the liver (oval cell infiltration, bile duct proliferation and cellular hypertrophy) accompanied tumor formation (1000, 1500 ppm); significantly increased liver weight (500-1500 ppm); significantly reduced body weight (500-1500 ppm)	Ito et al., 1975
Mouse/DDY	12-21 M/group	0 or 500 ppm diet for 16, 20, 24 or 36 weeks, then control diet for 0-36 weeks	growth, liver weight and gross, microscopic and ultrastructural examination of the liver	Increased liver weights probably because of the presence of tumors; other changes in the liver related to formation of benign and [illegible] (see Table 5-1)	Ito et al., 1976
Mouse/dd	20-38 M/group	0, 100, 250 or 500 ppm diet for 24 weeks	growth, liver weight and histological and ultrastructural examination of the liver	Significantly increased relative and absolute liver weight only at doses that produced tumors (250, 500 ppm); histological changes (oval cell infiltration and bile duct proliferation) only at doses that produced tumors (250, 500 ppm)	Ito et al., 1973a
Mouse/dd	20-30 M/group	0, 50, 100 or 250 ppm diet for 24 weeks	growth, liver weight, and histological examination of the liver	Significantly increased liver weight and histological changes (primarily cellular hypertrophy) only at a dose that also produced tumors (250 ppm)	Ito et al., 1973b

Fitzhugh et al. (1950) conducted a lifetime feeding study on Wistar rats, in which groups of 10 rats/sex were fed 0, 50, 100 or 800 ppm α-HCH in the diet until they died or were killed when moribund. Growth rate, food consumption, mortality, organ weights, and gross and microscopic pathology were examined. Microscopic analysis, however, was not performed on all rats (only on 8-15 rats/treatment) and detailed sections were not always prepared for those that were examined. There was no evidence of compound-induced development of tumors. Compared with controls, high-dose rats had significantly reduced survival, reduced growth rate, increased liver weight and histological evidence of slight to moderate kidney damage and moderate liver damage. Increased liver weights were also observed in rats fed 50 and 100 ppm, but no significant changes in liver histology were observed at these concentrations. No effects were observed among rats fed 10 ppm α-HCH. In a similar study, Ito et al. (1975) observed neoplastic changes in the livers of Wistar rats only at dietary levels $\geq$1000 ppm α-HCH.

5.5.2. β-HCH. Chronic and subchronic oral studies on β-HCH are summarized in Table 5-8. Three of the five studies (Ito et al., 1973a,b, 1975) were designed to investigate and characterize hepatic carcinogenic response in male Wistar rats and dd mice. Neoplastic changes were not observed in these studies, but increases in absolute and relative liver weight were observed at doses $\geq$250 ppm. Nonneoplastic histological changes were not observed. These studies were conducted only for 24-72 weeks.

In a 110-week dietary study on CF1 mice, Thorpe and Walker (1973) observed enlargement of the liver, but this effect was probably related to the development of tumors. No other significant compound-related effects were observed.

TABLE 5-8

Oral Toxicity Summary for β-HCH

Species/ Strain	No. and Sex/Group	Dose and Duration of Treatment	Endpoints Monitored	Effects	Reference
Rat/Wistar	10/sex/exposed group; 20 M, 20 F controls	0, 10, 100, 800 ppm diet for life	growth, food consumption, mortality, organ weights, gross pathology; microscopic pathology was conducted on only 5-14 animals/treatment	Significantly reduced survivorship (800 ppm) gross and histological evidence of liver damage (100, 800 ppm); significantly increased relative liver weight (10, 100, 800 ppm); significantly reduced body weight (100 ppm; 800 ppm rats survived only 4.4 ± 1.3 weeks and were not weighed); no tumors were observed	Fitzhugh et al., 1950
Rat/Wistar	10-24 M/group started on test; 5-8/group examined	0, 500 or 1000 ppm diet for 24, 48 or 72 weeks	growth, gross and histological examination of tissues with emphasis on the liver	Significantly reduced growth (500, 100 ppm); significantly increased relative and absolute liver weights (500, 1000 ppm); no neoplastic or nonneoplastic changes in any organ	Ito et al., 1975
Mouse/CF1	30/sex/exposed group; 45 M, 45 F controls	0 or 200 ppm diet for 110 weeks	mortality, clinical signs of toxicity, gross and histological examination of major organs	Liver enlargement, probably because of neoplastic changes	Thorpe and Walker, 1973
Mouse/dd	20 M/group	0, 100, 250 or 500 ppm diet for 24 weeks	growth, liver weight and histological and ultrastructural examination of the liver	Significantly increased relative and absolute liver weight (250, 500 ppm); no other effects	Ito et al., 1973a
Mouse/dd	20 M/group	0, 50, 100, 250 ppm diet for 24 weeks	growth, liver weight and histological and ultrastructural examination of the liver	Significantly increased relative and absolute liver weight (250 ppm); no other significant effects	Ito et al., 1973b

In a lifetime study, Fitzhugh et al. (1950) observed early mortality (average lifespan = 4.4±1.3 weeks), histological evidence of liver damage and increased relative liver weight in Wistar rats fed 800 ppm β-HCH. Significantly reduced body weight, increased relative liver weight and histological evidence of liver damage were observed among rats fed 100 ppm; increased relative liver weight was the only effect observed at 10 ppm. No tumors were observed at any level of treatment; however, only 5-14 rats/level of treatment were examined microscopically, and detailed examinations were not always prepared for those that were examined.

5.5.3. γ-HCH. Long-term oral studies on the toxicity of γ-HCH have been conducted on rats (Dikshith and Datta, 1977; Dikshith et al., 1978; NCI, 1977; Ito et al., 1975; Fitzhugh et al., 1950; Research and Consulting Co., Ltd., 1983; Oesch et al., 1982), mice (Oesch et al., 1982; Thorpe and Walker, 1973; Ito et al., 1973a,b), dogs (Rivett et al., 1978; Earl et al., 1970; Lehman, 1965) and monkeys (Santolucito, 1975) (Table 5-9). The studies conducted by NCI (1977) on rats and mice, by Ito et al. (1975) on rats and by Ito et al. (1973a,b) on mice were designed to investigate oncogenicity, but nonneoplastic effects were also investigated.

A number of long-term oral studies report that γ-HCH can cause hepatic hypertrophy, induce microsomal enzyme activity and cause nonneoplastic hepatic changes in the absence of neoplastic changes (Dikshith et al., 1978; Fitzhugh et al., 1950; Research and Consulting Co., Ltd., 1983; Oesch et al., 1982; Ito et al., 1973a; Rivett et al., 1978). If these studies, however, had used larger number of animals and were conducted for longer periods of time, it is possible that a carcinogenic response would have been observed, especially since γ-HCH has been shown to cause liver tumors in CF1 and dd mice (Thorpe and Walker, 1973; Hanada et al., 1973; Goto et al.,

TABLE 5-9

Oral Toxicity Summary for γ-HCH

Species/Strain	No. and Sex/Group	Dose and Duration of Treatment	Endpoints Monitored	Effects	Reference
Rat/ITRC	10 M/group	0 or 17.6 mg/kg/day in peanut oil for 90 days	clinical signs, mortality, gross and histological examination of testes and epididymis	1/10 treated vs. 0/10 controls died; necrosis of spermatogenic cells and giant cell formation	Dikshith and Datta, 1977
Rat/ITRC	16 M/group (150-175 g)	0 or 17.6 mg/kg/day in peanut oil for 90 days	clinical signs, mortality, histological examination of liver, kidney, testes and epididymis; SDH, ATPase, alkaline phosphatase and acid phosphatase activities were determined for liver, kidney and testes; AchE activity measured for brain and blood	Significantly reduced AchE activities in blood (45.83%) and brain (38.46%); significantly increased activities of SDH, ATPase and acid phosphatase in testes; significantly reduced SDH in liver and kidney, alkaline phosphatase in liver and acid phosphatase in liver and kidney; degenerative changes in testes (tubular atrophy, necrosis of spermatogenic cells, giant cell formation, enlargement of interstitial space) and liver (marked focal necrosis, congestion, swelling of hepatocytes, mild proliferation of fibroblasts around bile ducts)	Dikshith et al., 1978
Rat/Osborne-Mendel	50/sex/exposed group 10 M, 10 F matched controls 40 M, 40 F pooled controls	0, 236 or 472 ppm diet (males), 0, 135 or 270 ppm diet (females) for 80 weeks, then control diet for 29-30 weeks	clinical signs, growth, mortality, histological examination of all major tissues	None (Note: poor survival; only 40% female controls and 60, 50 and 48% of male control, low- and high-dose rats survived to the end of the study; deaths were not tumor-related)	NCI, 1977
Rat/Wistar	18-24 M/group started on test; only 6-8/group examined	0 or 500 ppm diet for 24 or 48 weeks	growth, gross and histological examination of tissues with emphasis on the liver	None	Ito et al., 1975
Rat/Wistar	10/sex/exposed group; 20/sex controls	0, 5, 10, 50, 100, 400, 800 or 1600 ppm diet in corn oil for life or 0, 10, 100 or 800 ppm diet (as powder) for life	growth, food consumption, mortality, organ weights, gross pathology; histological examination of 5-16 rats/group	Nervous symptoms and convulsions (800, 1600 ppm); significantly reduced survival (800, 1600 ppm in corn oil only); significantly reduced body weight (1600 ppm); significantly increased relative liver weight (800, 1600 ppm); slight to moderate liver damage (800, 1600 ppm); slight to moderate kidney damage (800 ppm, powder only)	Fitzhugh et al., 1950

TABLE 5-9 (cont.)

Species/Strain	No. and Sex/Group	Dose and Duration of Treatment	Endpoints Monitored	Effects	Reference
Rat/Wistar	20/sex/group	0, 0.2, 0.8, 4, 20, 100 ppm (0.29, 1.55, and 7.25 mg/kg bw for males and 0.33, 1.67 and 7.90 mg/kg bw for females fed 4, 20 and 100 ppm, respectively) for 12 weeks	mortality, body weight, food consumption, hematology, urinalysis, gross and histopathological examination of the liver	None at 0.2-0.8 ppm; liver hypertrophy and increased levels of cytochrome P-450 (4 ppm); histological changes in the liver and kidneys at 20 and 100 ppm; decreased weight gain at 100 ppm	Research and Consulting Co., Ltd., 1983
Rat/Osborne-Mendel	1-3/sex/group	0, 56, 111 or 360 ppm diet for 3 months	liver weight, liver microsomal enzyme activities	Significant increase in absolute and relative liver weight (females at 111 or 360 ppm; males at 360 ppm); dose-related increases in hepatic enzyme activities significant at all doses for 7-ethoxycoumarin-o-dealkylase, epoxide hydrolase, glutathione-S-transferase	Oesch et al., 1982
Mouse/CF1	1-3/sex/group	0, 56, 111 or 360 ppm diet for 3 months	liver weight, liver microsomal enzyme activities	Significant increase in absolute and relative liver weight (360 ppm); significant increases in ethoxycoumarin-o-dealkylase (all levels, males; 360 ppm, females), epoxide hydrolase (111 ppm, males; 360 ppm females), glutathione-S-transferase (all levels, females; 111 ppm, males), nonactivated UDP-glucuronosyl transferase (360 ppm, females)	Oesch et al., 1982
Mouse/CF1	29 M, 29 F exposed; 45 M, 44 F controls	0, 400 ppm diet for 110 weeks	mortality, clinical signs of toxicity, gross and histological examination of major organs	Liver enlargement related to tumor development	Thorpe and Walker, 1973
Mouse/B6C3F1	1-3/sex/group	0, 56, 170 or 270 ppm diet for 3 months	liver weight, liver microsomal enzyme activities	No effect on liver weight; all mice at 270 ppm died; significant increases in ethoxycoumarin-o-dealkylase (170 ppm), epoxide hydrolase (56 ppm, females; 170 ppm males and females), glutathione-S-transferase (170 ppm) nonactivated UDP-glucuronosyl transferase (170 ppm, females), activated UDP-glucuronosyl transferase (56, 170 ppm, males)	Oesch et al., 1982

TABLE 5-9 (cont.)

Species/Strain	No. and Sex/Group	Dose and Duration of Treatment	Endpoints Monitored	Effects	Reference
Mouse/B6C3F1	50 M, 50 F/treatment; 10 M, 10 F matched controls; 40 M, 40 F pooled controls	0, 80 or 160 ppm for 80 weeks, then control diet for 10-11 weeks	clinical signs, growth, mortality, histological examination of all major tissues	None	NCI, 1977
Mouse/dd	20 M/group	0, 100, 250 or 500 ppm diet for 24 weeks	growth, liver weight, histological and ultrastructural examination of the liver	500 ppm: reduced growth rate; significantly increased absolute and relative liver weight; no non-neoplastic or neoplastic histological changes at any dose	Ito et al., 1973a
Mouse/dd	20 M/group	0, 50, 100 or 250 ppm diet for 24 weeks	growth, liver weight, histological and ultrastructural examination of the liver	None	Ito et al., 1973b
Dog/beagle	4 M, 4 F/group	0, 25, 50 or 100 ppm diet for 104 weeks (0, 0.83, 1.60 or 2.92 mg/kg/day) 200 ppm diet for 32 weeks (dose not measured)	growth, food consumption, water intake, hematology, urinalysis, ophthalmoscopic examination, EEG, organ weights and histological examination of tissues, serum biochemistries	200 ppm: slightly enlarged liver, no histopathological findings; elevated serum alkaline phosphatase activity. 100 ppm: slightly enlarged liver, no histopathological findings; slightly elevated serum alkaline phosphatase activity. 25, 50 ppm: no effects	Rivett et al., 1978
Dog/NR	NR	7.5, 15.0 or 22.5 mg/kg/day in the diet for 24 weeks	hematology, serum alkaline phosphatase activity, histopathological examination of the liver	22.5 mg/kg/day: decreased numbers of reticulocytes and platelets, crenated RBCs and a myeloid: erythroid ratio >750:1. all doses: increased serum alkaline phosphatase; no histological findings	Earl et al., 1970
Dog/NR	2/sex/group	0 or 15 ppm diet for 63 weeks	mortality, growth, organ weights, hematology, histopathology	None	Lehman, 1965
Monkey/squirrel	NR	0.05 mg/kg/day, 6 days/week for 3 years	EEG recordings made for 15 minutes during anesthetized sleep	No clinically significant changes	Santolucito, 1975

NR = Not reported

1972) and since the nonneoplastic changes have been associated with the development of tumors in rats and mice exposed to α-HCH and T-HCH (Ito et al., 1975, 1976; Schulte-Hermann and Parzefall, 1981; Munir et al., 1983; Nigam et al., 1982; 1984b). Although negative results were found for oncogenicity in the Fitzhugh et al. (1950) and NCI (1977) lifetime studies, Fitzhugh et al. (1950) examined only a portion of the treated rats in the study (criteria for selection not reported), and the NCI (1977) study yielded negative results for both neoplastic and nonneoplastic effects.

Two studies have reported that γ-HCH adversely affects the kidney. Fitzhugh et al. (1950) reported gross and histological evidence of slight to moderate kidney damage (focal nephritis, hyaline granular degeneration, pitted kidneys) in rats fed 800 ppm γ-HCH as powder mixed in the diet for life but not in rats treated similarly with 800 or 1600 ppm dietary γ-HCH dissolved in corn oil. The Research and Consulting Co., Ltd., (1983) observed tubular degeneration, hyaline droplets, tubular casts, tubular distension, interstitial nephritis and basophilic tubules in Wistar KFM-HAN SPF rats fed 20 or 100 ppm γ-HCH (1.55 or 7.25 mg/kg/day) for 12 weeks, but not in rats exposed similarly to 0.2, 0.8 or 4 ppm γ-HCH.

Dikshith and Datta (1977) and Dikshith et al. (1978) demonstrated that γ-HCH (17.6 mg/kg/day in peanut oil for 90 days) can cause testicular atrophy in ITRC rats.

Fitzhugh et al. (1950) observed nervous symptoms and convulsions in rats fed 800 or 1600 ppm γ-HCH for life. Dikshith et al. (1978) reported significant decreases in AchE activity in the blood and brains of ITRC rats given 17.6 mg γ-HCH/kg/day in peanut oil for 90 days. Shorter-term studies also suggested that γ-HCH causes neurotoxic effects. Desi (1974) reported that the number of lever presses in an operant conditioning box were significantly increased in Wistar rats exposed orally to 25 mg γ-HCH/kg/day for 40 days; an increased number of errors in maze-running and increased maze-running times were observed in rats treated similarly at doses ≥5 mg/kg/day. Müller et al. (1981) reported significantly reduced conduction velocity in Wistar rats fed 25 mg γ-HCH/kg/day for 30 days.

Czegledi-Janko and Avar (1970) reported that male workers in a fertilizer plant with "mild but definite" symptoms of neurotoxicity (clinical exam and EEG) had ≥0.02 ppm γ-HCH in their blood; however, 22 of the 37 men in the study had been exposed to aldrin 2 years before their examination. Examinations of these men before γ-HCH exposure revealed a strong association between exposure to aldrin and neurotoxic effects.

Hematological effects resulting from exposure to γ-HCH have also been reported. Earl et al. (1970) reported that adverse hematological effects (decreased numbers of reticulocytes and platelets, crenated RBCs and a myeloid:erythroid ratio >750:1) occurred in dogs fed 225 mg γ-HCH/kg/day in the diet for 24 weeks. These effects were not reported for dogs fed 7.5 or 15.0 mg/kg/day. A case-report (Morgan et al., 1980) also suggests that anemia may result from prolonged exposure to γ-HCH; severe but reversible hypoplastic anemia was observed in a 2.5-year-old boy who was exposed to γ-HCH since birth through use of a vaporizor in his home. Other family members were not affected.

Short-term studies suggest that γ-HCH may cause immunosupression. A dose-related decrease in immunological titers was observed in rabbits gavaged with 1.5-12 mg γ-HCH/kg/day, 5 days/week for 5-6 weeks, then challenged with S. typhimurium (Desi et al., 1978). Similar results were reported in rats exposed orally to either 6.25 or 24 mg γ-HCH/kg in olive oil on alternate days for 35 days (Dewan et al., 1980).

5.5.4. δ-HCH. Long-term oral studies on δ-HCH are summarized in Table 5-10. Significant compound-related changes were not observed in male Wistar rats fed 500 or 1000 ppm δ-HCH for up to 48 months (Ito et al., 1975). Ito et al. (1973a) observed significant elevation in relative and absolute liver weights among male dd mice fed 500 ppm δ-HCH for 24 weeks; however, no histological or ultrastructural changes were observed in the livers of these mice. No effects on the liver were observed in mice fed 100 or 250 ppm δ-HCH for 24 weeks.

5.5.5. ε-HCH. Pertinent data regarding the chronic toxicity of ε-HCH could not be located in the available literature as cited in the Appendix.

5.5.6. T-HCH. Long-term oral studies on the toxicity of T-HCH have been conducted on rats (Fitzhugh et al., 1950; Barros and Saliba, 1978; Barros et al., 1982; Shivanandappa and Krishnakumari, 1981, 1983; Shivanandappa et al., 1982) and mice (Nigam et al., 1979, 1982, 1984a,b; Munir and Bhide, 1984; Kashyap et al., 1979). These studies are summarized in Table 5-11.

A number of these studies have shown that T-HCH has adverse effects upon the liver (Fitzhugh et al., 1950; Barros and Saliba, 1978; Barros et al., 1982; Shivanandappa and Krishnakumari, 1981; Nigam et al., 1982, 1984a,b; Munir and Bhide, 1984). These effects include increased relative and absolute weight of the liver and histological (cellular alterations, degenerative and proliferative changes, glycogen accumulation), ultrastructural and histochemical changes. Barros and Saliba (1978) reported T-HCH-induced changes in the livers of Wistar rats exposed to as little as 0.9 ppm for 90 days. In general, these changes increased in incidence and severity in proportion to dose and duration of treatment. Nigam et al. (1982, 1984a,b) and Munir and Bhide (1984) demonstrated that the progression of hepatic

TABLE 5-10

Oral Toxicity Summary for δ-HCH

Species/ Strain	No. and Sex/Group	Dose and Duration of Treatment	Endpoints Monitored	Effects	Reference
Mouse/dd	20 M/group	0, 100, 250 or 500 ppm diet for 24 weeks	growth, liver weight and histological and ultrastructural examination of the liver	Significantly increased relative and absolute liver weight (500 ppm); no histological or ultrastructural changes in the liver	Ito et al., 1973a
Rat/Wistar	18-24 M/group started on test; only 5-8/group examined	0, 500 or 1000 ppm diet for 24 or 48 weeks	growth, gross and histological examination of tissues with emphasis on the liver	Slight reduction in growth; no significant gross or histological changes in the liver; slight increase in relative and absolute liver weights (statistical significance is questionable since standard deviation was not reported)	Ito et al., 1975

TABLE 5-11

Oral Toxicity Summary for T-HCH

Species/ Strain	No. and Sex/Group	Dose and Duration of Treatment	Endpoints Monitored	Effects	Reference
Rat/Wistar	10/sex/group exposed; 20/sex controls	0, 10, 100 or 800 ppm diet for life	growth, food consumption, mortality, organ weights, gross pathology; histological examinations were conducted on 9-11 animals/group	Significantly decreased survival and growth (800 ppm); significantly increased relative liver weight (100, 800 ppm); slight to moderate histological changes in liver (100, 800 ppm); slight histological changes in kidney (800 ppm); gross and histological evidence of testicular atrophy (800 ppm)	Fitzhugh et al., 1950
Rat/Wistar	10/NR/group	0, 0.9 or 900 ppm diet for 90 days	growth, blood glucose, hepatic glucose-6-phosphate dehydrogenase, histological examination of liver, kidneys, heart, spleen and brain	Significantly reduced growth and increased relative liver weight (900 ppm); histological evidence of degenerative liver changes (0.9 and 900 ppm) and kidney changes (900 ppm)	Barros and Saliba, 1978
Rat/NR	NR	0 or 900 ppm for 60 or 90 days	hepatic and renal alkaline and acid phosphatase activities	Reduced activities of alkaline phosphatase in kidney (32 and 40% reduction after 60 and 90 days, respectively) and liver (46 and 37% reduction after 60 and 90 days, respectively)	Barros et al., 1982
Rat/CFT-Wistar	10 M/group	0, 100, 250, 750, 1500 or 3000 ppm diet for 90 days	growth, food consumption, mortality, serum biochemistry, organ weights, histological examination of major organs, histochemistry of liver and adrenals, liver biochemistry	100% mortality at 3000 ppm, accompanied by signs of CNS stimulation; 2/10 deaths at 1500 ppm; significantly reduced food consumption and growth (1500 ppm); significant and dose-related increases in relative weights of liver, kidneys and heart (all concentrations); significantly increased relative adrenal weight (750, 1500 ppm), brain weight (1500 ppm) and spleen weight (750 ppm); significantly reduced relative testicular weight (1500 ppm); histological changes in the liver ($\geq$250 ppm), adrenals (750 and 1500 ppm) and testes (1500 ppm); histochemical and biochemical evidence of liver damage ($\geq$250 ppm)	Shivanandappa and Krishnakumari, 1981

TABLE 5-11 (cont.)

Species/ Strain	No. and Sex/Group	Dose and Duration of Treatment	Endpoints Monitored	Effects	Reference
Rat/CFT-Wistar	10 M/group	0, 100, 250, 750 or 1500 ppm for 90 days	food consumption, growth rate, organ weights, histological and histochemical examination of adrenals	Reduced food consumption and growth (1500 ppm); histological and histochemical evidence of steroidogenic inhibition in the adrenal cortex (750, 1500 ppm); adrenal hypertrophy (750, 1500 ppm)	Shivanandappa et al., 1982
Rat/CFT-Wistar	10 M/group	0, 100, 750 or 1500 ppm (0, 80, 625 or 1174 mg/rat/90 days) for 90 days	growth, food consumption and histology, histochemistry and lipid/cholesterol content of the testes	Significant effects only at 1500 ppm; these include mortality (2/10), reductions in growth and food consumption (7-13 weeks), decreased testicular weight, decreases in seminiferous tubule and Leydig cell diameters, decreased testicular enzyme activities and increases in total lipid and total cholesterol content of the testes	Shivanandappa and Krishnakumari, 1983
Mouse/Swiss	6 M/group killed at monthly intervals	0 or 500 ppm diet for up to 10 months	organ weights and histological examination of tissues (it is unclear what tissues were actually examined; the report focuses on testicular changes)	Significantly increased testicular weight (≥3 months exposure); significant degenerative changes in the seminiferous epithelium and "spermatagonia cells"; no other effects reported	Nigam et al., 1979
Mouse/Swiss	6 M,F/group killed at 10, 20 and 30 days, then at monthly intervals	0 or 500 ppm diet for 60 months	liver weight and histopathology	Compound-related gross and histological changes in the liver, proportional to duration of treatment; neoplastic nodules developed in the last 3 months of treatment	Nigam et al., 1982
Mouse/Swiss	6 M/group killed after 2, 4, 6 or 8 months treatment; 75 controls	0 or 500 ppm diet for 2, 4, 6 or 8 months or 2, 4, 6 or 8 months plus 4 months control diet or 2, 4, 6 or 8 months plus 10 months control diet	growth and gross, histological, ultrastructural and histochemical analysis of the liver	Liver weight increased with duration of exposure, then tended to decrease upon discontinuation of exposure; compound-related progression of histological and ultrastructural changes leading to tumor development; histochemically-defined accumulation of glycogen and iron in liver cells; these changes were reversible if treatment was discontinued before neoplastic changes occurred	Nigam et al., 1984a,b

TABLE 5-11 (cont.)

Species/ Strain	No. and Sex/Group	Dose and Duration of Treatment	Endpoints Monitored	Effects	Reference
Mouse/Swiss	NR/M	0 or 500 ppm for 3, 7 or 10 months	liver histology and ornithine metabolism	Compound-related progression of histologic changes resulting in the development of tumors; necrosis (3 months), adenomatous nodules (7 months) and hepatocellular carcinoma (nearly all animals after 10 months of treatment); exact numbers not reported); changes in ornithine metabolism associated with above histological changes	Munir and Bhide, 1984
Mouse/Swiss	30/sex/group	0, 10 mg/kg/day (olive oil) or 100 ppm diet for 100 weeks	mortality, growth, food consumption, clinical signs of toxicity; gross and histological examination of all major organs (emphasis on tumors)	Signs of intoxication (convulsions and tendency to circle in one direction with drooping ears; corneal opacity during latter portion of study; increased incidence of animals with liver tumors and in total number of animals with tumors (not a well-reported study)	Kashyap et al., 1979

NR = Not reported

changes caused by T-HCH leads ultimately to the development of tumors and are reversible only if exposure ceases at the very earliest stages sometime before tumor formation.

High doses of T-HCH have been shown to cause kidney damage in Wistar rats. Fitzhugh et al. (1950) reported focal nephritis (tubular atrophy and hyaline cast formation), brown pigmentation and basal vacuolization in the kidneys of rats fed 800 ppm T-HCH for life. Barros and Saliba (1978) also reported hyaline degeneration in the kidneys of rats exposed to 900 ppm for 90 days. Barros et al. (1982) reported a 40% reduction in renal alkaline phosphatase activity after 90 days of exposure. Shivanandappa and Krishnakumari (1981) observed increased relative kidney weight but no histological changes in male CFT-Wistar rats fed 750 or 1500 ppm T-HCH for 90 days.

Dietary T-HCH has been shown to cause testicular atrophy in rats and mice. These effects were observed in rats fed 1500 ppm for 90 days (Shivanandappa and Krishnakumari, 1981, 1983) or 800 ppm for life (Fitzhugh et al., 1950), and in mice fed 500 ppm for up to 10 months (Nigam et al., 1979). Testicular effects were not seen in rats fed 10, 100 or 750 ppm; lower concentrations were not tested in mice.

In two separate studies, Shivanandappa and Krishnakamuri (1981) and Shivanandappa et al. (1982) observed increased adrenal weight and histological and histochemical evidence of steroidogenic inhibition in the adrenal cortex of male CFT-Wistar rats fed $\geq$750 ppm T-HCH for 90 days. Adrenal changes were not observed in rats fed $\leq$250 ppm.

Two oral studies suggest that T-HCH may cause neurotoxic effects. In a 90-day study, Shivanandappa and Krishnakumari (1981) reported 100% mortality in male CFT-Wistar rats fed 3000 ppm which was accompanied by signs of CNS stimulation; signs of CNS stimulation were not reported in rats fed $\leq$1500 ppm. Histological or ultrastructural changes in the nervous system were not examined. Kashyap et al. (1979) observed convulsions and a "tendency to circle in one direction with drooping ears" among Swiss mice fed 100 ppm in the diet or gavaged with 10 mg/kg/day for 100 weeks. These signs of intoxication were said to be "not prominent." Kashyap et al. (1979) also reported uni- and bilateral corneal opacity in the T-HCH-exposed mice.

5.6. OTHER RELEVANT INFORMATION

Oral LD_{50}s for isomers of HCH are summarized in Table 5-12.

5.7. SUMMARY

5.7.1. α-HCH. Dietary α-HCH has been shown to cause increased incidences of liver tumors in five strains of mice (Ito et al., 1973a,b, 1976; Nagasaki et al., 1972a, 1975; Hanada et al., 1973; Goto et al., 1972) and in Wistar rats (Ito et al., 1975; Schulte-Hermann and Parzefall, 1981). The teratogenic and reproductive effects of α-HCH have not been investigated. Nonneoplastic hepatic changes have been observed in rats and mice fed α-HCH (Schulte-Hermann and Parzefall, 1981; Ito et al., 1973a,b, 1975, 1976; Fitzhugh et al., 1950).

5.7.2. β-HCH. Dietary β-HCH has been shown to cause definite increased incidences of liver tumors in CF1 mice (benign and malignant) and possibly a marginal increase in ICR-JCL mice (hepatomas) (Thorpe and Walker, 1973; Goto et al., 1972) but clearly not in dd mice (Ito et al., 1973a,b; Hanada et al., 1973; Nagasaki et al., 1972a) nor in Wistar rats (Ito et al., 1975; Fitzhugh et al., 1950). The reproductive and teratogenic effects of β-HCH have not been investigated. Nonneoplastic and neoplastic histological changes in the liver were not observed in studies that were designed to investigate hepatic carcinogenic response (Ito et al., 1973a,b, 1975); increases in absolute and relative liver weight were observed at dietary

TABLE 5-12

Oral LD_{50} Values for Isomers of HCH*

Isomer	Species	LD_{50} (mg/kg)
α-HCH	mouse	1000
	rat	500-1700
β-HCH	mouse	1500
	rat	2000
γ-HCH	mouse	86
	rat	124-230
	rabbit	60-200
	guinea pig	100-127
δ-HCH	rat	750-1000
Mixture of isomers (proportions not reported)	rat	600-1250
	mouse	700

*Source: WHO, 1969

concentrations $\geq$250 ppm. Fitzhugh et al. (1950) observed increases in liver weight accompanied by histological changes in rats fed $\geq$100 ppm β-HCH; increased relative liver weight was the only effect observed at 10 ppm. Early mortality was also observed among rats fed 800 ppm. No tumors were observed in this study; however, not all of the rats started on the test were examined histologically (no criterion for selection was given). No other chronic effects were reported.

5.7.3. γ-HCH (Lindane). Dietary γ-HCH was shown to cause an increased incidence of liver tumors in male CF1 mice fed 400 ppm for 110 weeks (Thorpe and Walker, 1973), a marginal response in male dd mice fed 600 ppm for 32 weeks and then examined 5-6 weeks posttreatment (Hanada et al., 1973), and a marginal response in male ICR-JCL mice fed 600 ppm for 26 weeks (Goto et al., 1972). No liver tumors were observed in dd mice fed up to 500 ppm for 24 weeks (Ito et al., 1973a,b; Nagasaki et al., 1972a) or in Wistar rats fed 500 ppm for up to 48 weeks (Ito et al., 1975). Significant compound-related development of tumors of any type was not observed in NMRI mice treated with γ-HCH for 80 weeks (Herbst et al., 1975; Weisse and Herbst, 1977), B6C3F1 mice also treated for 50 weeks (NCI, 1977), Osborne-Mendel rats (NCI, 1977) or Wistar rats (Fitzhugh et al., 1950). The study conducted by NCI (1977) has been criticized for poor survival of rats, changes in dosing regimen and the possibility that male rats did not receive MTDs (IARC, 1979). The negative findings of Fitzhugh et al. (1950) are also inconclusive since only small numbers of animals were examined histologically. The negative findings of Ito et al. (1973a,b), Nagasaki et al. (1972a) and Ito et al. (1975) might be attributed to small numbers of animals and short duration. A metabolite of lindane, 2,4,6-trichlorophenol, has been identified in exposed rodents and humans and is considered to have a weight-of-evidence for human carcinogenicity of Group B2.

Orally-administered γ-HCH was not found to be teratogenic or fetotoxic in Wistar rats (Khera et al., 1979), CD rats (Palmer et al., 1978a), CFY rats (Palmer et al., 1978b), New Zealand White rabbits (Palmer et al., 1978b) or CD-1 mice (Chernoff and Kavlock, 1983; Gray and Kavlock, 1984). In contrast, a study by Dzierzawski (1977) reported increased numbers of resorbed fetuses in hamsters (40 mg/kg on day 9 of gestation), rabbits (40 or 60 mg/kg on day 9 of gestation) and rats (40, 50 or 100 mg/kg on various days of gestation). Maternal toxicity was not reported. These doses are higher than any of those tested in the negative studies of γ-HCH, though Chernoff and Kavlock (1983) reported that 25 mg/kg/day was the maximum dose that was not toxic to maternal CD-1 mice.

Palmer et al. (1978a) failed to observe adverse effects on reproduction in three generations of CD rats fed up to 100 ppm γ-HCH in the diet. Dikshith and Datta (1977) and Dikshith et al. (1978), however, observed testicular atrophy in ITRC rats gavaged with 17.6 mg γ-HCH/kg in peanut oil for 90 days, suggesting that γ-HCH might have adverse effects upon reproduction.

Long-term oral studies have associated exposure to HCH with nonneoplastic liver changes (Dikshith et al., 1978; Fitzhugh et al., 1950); Research and Consulting Co., Ltd., 1983; Oesch et al., 1982; Ito et al., 1973a, Rivett et al., 1978), kidney changes (Fitzhugh et al., 1950; Research and Consulting Co., Ltd., 1983), hematological effects (Earl et al., 1970; Morgan et al., 1980) and neurotoxicity (Fitzhugh et al., 1950; Czegledi-Janko and Avar, 1980). Short-term studies suggest that γ-HCH may cause immunosupression (Dewan et al., 1980; Desi et al., 1978).

5.7.4. δ-HCH. Dietary δ-HCH did not cause neoplastic or nonneoplastic changes in the livers of male dd mice (Ito et al., 1973a; Nagasaki et al., 1972a) or male Wistar rats (Ito et al., 1975). These studies used small numbers of animals and were only conducted for 24 weeks. A mixture of δ- and ε-HCH caused benign and malignant hepatomas in male ICR-JCL mice when fed in the diet at 600 ppm for 26 weeks (Goto et al., 1972). Other pertinent data regarding the teratogenic, reproductive or chronic effects of δ-HCH could not be located in the available literature as cited in the Appendix.

5.7.5. ε-HCH. A mixture of δ- and ε-HCH caused benign and malignant hepatomas in male ICR-JCL mice when fed in the diet at 600 ppm for 26 weeks (Goto et al., 1972). Other pertinent data regarding the health effects associated with exposure to ε-HCH could not be located in the available literature as cited in the Appendix.

5.7.6. T-HCH. T-HCH has been shown to cause increased incidences of liver neoplasms in four strains of mice (Hanada et al., 1973; Goto et al., 1972; Kashyap et al., 1979; Nigam et al., 1984a; Bhatt et al., 1981; Munir et al., 1983; Nagasaki et al., 1971, 1972b; Nagasaki, 1973; Munir and Bhide, 1984) but not in Wistar rats (Munir et al., 1983) or Syrian golden hamsters (Munir et al., 1983).

The teratogenic effects of T-HCH have not been investigated. Nigam et al. (1979) and Shivanandappa and Krishnakumari (1981, 1983) have shown that orally-administered T-HCH causes testicular atrophy in rats and mice (≥800 ppm, rats; 500 ppm, mice).

Long-term oral administration of T-HCH has been shown to cause adverse effects on the liver (Fitzhugh et al., 1950; Barros and Saliba, 1978; Barros et al., 1982; Shivanandappa and Krishnakumari, 1981; Nigam et al., 1982, 1984a,b; Munir and Bhide, 1984), kidney (Fitzhugh et al., 1950, Barros and Saliba, 1978; Barros et al., 1982; Shivanandappa and Krishnakumari, 1981), adrenal cortex (Shivanandappa and Krishnakumari, 1981; Shivanandappa et al., 1982) and CNS (Shivanandappa and Krishnakumari, 1981; Kashyap et al., 1979). Kashyap et al. (1979) also reported that long-term oral exposure to T-HCH was associated with increased corneal opacity.

It has been proposed that in sensitive species/strains the nonneoplastic changes in the liver associated with exposure to certain isomers of HCH or to T-HCH are associated with neoplastic development. In some studies, clear progression of hepatic changes that ultimately lead to the development of malignant tumors has been observed at gross, histological and ultrastructural levels of examination. These changes are proportional to dose and duration of treatment and appear to be reversible only at the very earliest stages sometime before the development of nodular hyperplasia (Ito et al., 1975, 1976; Schulte-Hermann and Parzefall, 1981; Munir et al., 1983; Munir and Bhide, 1984; Nigam et al., 1982, 1984a; Sugihara et al., 1975). Although nodular hyperplasia may appear to regress shortly after HCH treatment is discontinued, if the observation period is extended, the development of hepatocellular carcinoma becomes apparent (Sugihara et al., 1975) (see Tables in Sections 5.1. and 9.2.). Sugihara et al. (1975) postulated that surviving cells from areas of nodular hyperplasia ultimately progress to hepatocellular carcinoma. As such, tissues affected by HCH would have "memory" to later respond in a recurrent manner to further HCH treatment or to another tumor progressor producing an additive carcinogenicity testing with cancer-positive HCH isomers.

6. AQUATIC TOXICITY

T-HCH is a mixture of the five HCH isomers in the following ranges: α-, 55-70%; β-, 6-8%; γ-, 10-18%; δ-, 3-4%; and trace amounts of the ε-isomer. The γ-isomer has insecticidal properties and preparations containing at least 99% γ-HCH are called lindane. The γ-isomer is considered to be the most important since it is the most toxic to aquatic organisms (U.S. EPA, 1980b).

6.1. ACUTE

Since there is a large volume of information dealing with acute toxicity of HCH to freshwater animals, only acute toxicity data pertinent to fish and invertebrate species found in North American waters will be presented. Exceptions may be made if data for other species provide general information regarding HCH toxicity (relative toxicity of the various isomers).

Information concerning toxicity of lindane to freshwater fish and amphibians is shown in Table 6-1. The most sensitive species was the brown trout, Salmo trutta, which had a 96-hour LC_{50} of 1.7 μg/ℓ (Johnson and Finley, 1980), the lowest reported acutely toxic concentration. The data in Table 6-1 indicate that salmonids generally are more sensitive to lindane than other species.

Data concerning the acute toxicity of HCH isomers other than lindane (γ-HCH) to freshwater fishes and amphibians are shown in Table 6-2. Sufficient information is not available to draw conclusions about the relative toxicity of other HCH isomers, but they appear to be less toxic than lindane. The mixture of isomers referred to as HCH is much less toxic than lindane. This is not only due to a lower γ-HCH content than pure lindane; it is possible that the other isomers either reduce the solubility of γ-HCH or somehow antagonize its toxicity (U.S. EPA, 1980b).

TABLE 6-1

Acute Toxicity of Lindane to Freshwater Vertebrates

Species	Concentration (μg/ℓ)	Effect	Reference
		FISH	
Rainbow trout *Salmo gairdneri*	38	96-hour LC_{50}	Katz, 1961
	22	96-hour LC_{50}, fry	Tooby and Durbin, 1975
	30	96-hour LC_{50}, yearlings	
	27	96-hour LC_{50}	Macek and McAllister, 1970
	18	96-hour LC_{50}, fry	Tooby et al., 1975
	40	detection limit, respiratory behavior	Slooff, 1979
	2	NOEC, respiratory behavior	Slooff, 1979
	22	48-hour EC_{50}	Pimentel, 1971
	20-25	lethal	McKee and Wolf, 1963
	32	96-hour LC_{50}	McLeay, 1976
	60	96-hour LC_{50}	Kanazawa, 1981
Brown trout *Salmo trutta*	2	96-hour LC_{50}	Macek and McAllister, 1970
	1.7	96-hour LC_{50}	Johnson and Finley, 1980
	20	lethal	McKee and Wolf, 1963
Lake trout *Salvelinus ramaycush*	32	96-hour LC_{50}	Johnson and Finley, 1980
Brook trout *Salvelinus fontinalis*	26	1.5-year LC_{50}	Macek et al., 1976
	8.8	MATC	
	44.3	LC_{50}	Macek et al., 1976
	26	11-day LC_{50}	Macek et al., 1976
Coho salmon *Oncorhynchus kisutch*	41	96-hour LC_{50}	Macek and McAllister, 1970
	50	96-hour LC_{50}	Katz, 1961
	23	96-hour LC_{50}	Johnson and Finley, 1980
Chinook salmon *Oncorhynchus tshamytsha*	40	96-hour LC_{50}	Katz, 1961
Goldfish *Carassius auratus*	131	96-hour LC_{50}	Macek and McAllister, 1970
	152	96-hour LC_{50}	Henderson et al., 1959
	120	48-hour LC_{50}	Hashimoto and Nishiuchi, 1981

TABLE 6-1 (cont.)

Species	Concentration (μg/ℓ)	Effect	Reference
		FISH (cont.)	
Carp *Cyprinus carpio*	170	48-hour LC_{50}, emulsifiable concentrate	Hashimoto and Nishiuchi, 1981
	950	48-hour LC_{50}, wettable powder	Hashimoto and Nishiuchi, 1981
	1300	48-hour LC_{50}, dust	Hashimoto and Nishiuchi, 1981
	1700	48-hour LC_{50}, granular	Hashimoto and Nishiuchi, 1981
	90	96-hour LC_{50}	Macek and McAllister, 1970
	1.28	safe concentration	Singh et al., 1981
	58	96-hour LC_{50}	Elezovic and Mitrovic-Tutundzic, 1981
	100	disruption of lipid metabolism, 24 hours	Freimane and Grundule, 1976
	200	96-hour LC_{50}	Chin and Sudderuddin, 1979
	310	48-hour LC_{50}	Kanazawa, 1981
Golden shiner *Notemigonus crysoleucas*	62-125	lethal threshold	Meyer, 1965
Fathead minnow *Pimephales promelas*	87	96-hour LC_{50}	Macek and McAllister, 1970
	56-62	96-hour LC_{50}	Henderson et al., 1959
	62-76	11-day LC_{50}	Macek et al., 1976
Black bullhead *Ictalurus melas*	64	96-hour LC_{50}	Macek and McAllister, 1970
Channel catfish *Ictalurus punctatus*	44	96-hour LC_{50}	Macek and McAllister, 1970
Tilapia *Tilapia mossambica*	3199	48-hour LC_{50}	Basha et al., 1984
	50	hematological effects, 6 days	Madhu et al., 1984
Guppy *Poecilia reticulata*	138	96-hour LC_{50}	Henderson et al., 1959
	16	96-hour LC_{50}	Gupta et al., 1984
Mosquitofish *Gambusia affinis*	74	48-hour LC_{50}, susceptible population	Culley and Fergusson, 1969
	3104	48-hour LC_{50}, resistant population	Culley and Fergusson, 1969
Bluegill *Lepomis macrochirus*	37-54	96-hour LC_{50}	Macek et al., 1969
	68	96-hour LC_{50}	Macek and McAllister, 1970
	77	96-hour LC_{50}	Henderson et al., 1959
	29-31	21-day LC_{50}	Macek et al., 1976
	25-65	96-hour LC_{50}	Cope, 1965
	57	96-hour LC_{50}, technical material	Randall et al., 1979
	138	96-hour LC_{50}, 1% dust	Randall et al., 1979

TABLE 6-1 (cont.)

Species	Concentration (μg/ℓ)	Effect	Reference
		FISH (cont.)	
Green sunfish *Lepomis cyanellus*	83	96-hour LC_{50}	Johnson and Finley, 1980
Redear sunfish *Lepomis macrolophus*	83	96-hour LC_{50}	Macek and McAllister, 1970
Largemouth bass *Micropterus salmoides*	32	96-hour LC_{50}	Macek and McAllister, 1970
Yellow perch *Pereco flavescens*	68	96-hour LC_{50}	Macek and McAllister, 1970
Stickleback *Gastorosteus aculeatus*	44-50	96-hour LC_{50}	Katz, 1961
		AMPHIBIANS	
Tadpole *Pseudacris triseriata*	2700	96-hour LC_{50}	Sanders, 1970
Bufo woodhousii	4400	96-hour LC_{50}	Sanders, 1970

TABLE 6-2

Acute Toxicity of Other HCH Isomers to Freshwater Vertebrates

Species	Chemical	Concentration (μg/ℓ)	Effect	Reference
			FISH	
Fish (unspecified)	β-HCH	2,000	toxic	McKee and Wolf, 1963
Fish (unspecified)	δ-HCH	200	toxic	McKee and Wolf, 1963
Rainbow trout *Salmo gairdneri*	HCH	18	96-hour LC_{50}	Johnson and Finley, 1980
	α-HCH	1,050	96-hour LC_{50}	Canton et al., 1975
Cutthroat trout *Salmo clarki*	HCH	9	96-hour LC_{50}	Johnson and Finley, 1980
Trout (unspecified)	β-HCH	500	toxicity threshold, fingerlings	McKee and Wolf, 1963
	δ-HCH	50	toxicity threshold, fingerlings	McKee and Wolf, 1963
Coho salmon *Oncorhynchus kisutch*	HCH	200	48-hour LC_{50}	Velson and Alderdice, 1967
Carp *Cyprinus carpio*	HCH	300	growth inhibited, 2 weeks	Takeda, 1978
	HCH	128	96-hour LC_{50}	Singh et al., 1981
Goldfish *Carassius auratus*	HCH	15,000	96-hour LC_{50}	Henderson et al., 1959
	HCH	2,300	96-hour LC_{50}	Tarzwell, 1959
	HCH	348	96-hour LC_{50}	Johnson and Finley, 1980
Fathead minnow *Pimephales promelas*	HCH	13,000-15,000	96-hour LC_{50}	Henderson et al., 1959
	HCH	2,000-2,300	96-hour LC_{50}	Tarzwell, 1959
	HCH	125	96-hour LC_{50}	Johnson and Finley, 1980
Channel catfish *Ictalurus punctatus*	HCH	105	96-hour LC_{50}	Johnson and Finley, 1980
Mosquitofish *Gambusia affinis*	HCH	1350	96-hour LC_{50}	Joshi and Rege, 1980

TABLE 6-2 (cont.)

Species	Chemical	Concentration (µg/ℓ)	Effect	Reference
		FISH (cont.)		
Guppy *Poecilia reticulata*	HCH	14,000	96-hour LC_{50}	Henderson et al., 1959
	HCH	2,170	96-hour LC_{50}	Tarzwell, 1959
	α-HCH	800-1,300	96-hour LC_{50}	Canton et al., 1975, 1978
	δ-HCH	2,000	death in 48 hours	McKee and Wolf, 1963
Bluegill *Lepomis macrochirus*	HCH	5,100	96-hour LC_{50}	Henderson et al., 1959
	HCH	790	96-hour LC_{50}	Tarzwell, 1959
	HCH	67	96-hour LC_{50}	Johnson and Finley, 1980
Largemouth bass *Micropterus salmoides*	HCH	41	96-hour LC_{50}	Johnson and Finley, 1980
Tilapia *Tilapia mossambica*	HCH	3,199	48-hour LC_{50}	Basha et al., 1983
		AMPHIBIANS		
Tadpole *Bufo woodhousii*	HCH	3,200	96-hour LC_{50}	Sanders, 1970
Microhyla ornata	HCH	7,270	96-hour LC_{50}	Pawar and Katdare, 1983

Data concerning the acute toxicity of HCH to marine fishes are shown in Table 6-3. The lowest reported lethal concentration was 7.3 μg/ℓ lindane, the 96-hour LC_{50} for the striped bass, Morone saxatilis (Korn and Earnest, 1974). The only data for HCH compounds other than lindane indicated that HCH was less toxic than lindane to the pinfish, Lagodon rhomboides, with 96-hour LC_{50} values of 86.4 μg/ℓ for HCH and 30.6 μg/ℓ for lindane (Schimmel et al., 1977).

Acute toxicity of HCH to fishes is not greatly influenced by temperature or water hardness. In experiments where temperature effects have been demonstrated, the results are conflicting. Lindane LC_{50} values for rainbow trout decreased 2.3 times over the temperature range of 2-18°C, but bluegill LC_{50} values increased 2.6 times over the range of 7-29°C (Johnson and Finley, 1980). Macek et al. (1969) also reported that lindane toxicity to bluegills increased slightly with increasing temperature, with 96-hour LC_{50} values of 54 μg/ℓ at 12.7°C and 37 μg/ℓ at 23.8°C. Acute toxicity to eels, Angiulla angiulla, decreased slightly at higher temperatures (48-hour LC_{50} = 600 μg/ℓ at 11.5°C and 1000 μg/ℓ at 22.5°C), which was attributed to increased mucus production at the higher temperature, thereby inhibiting pesticide uptake (Foulquier et al., 1971). Variations in water hardness have been found to have little or no effect on toxicity of lindane or HCH to fishes (Henderson et al., 1959; Johnson and Finley, 1980).

It is likely that insecticide-resistant populations of aquatic organisms can develop in areas where organochloride pesticides have been used for long periods. Culley and Ferguson (1969) studied this phenomenon in mosquitofish, Gambusia affinis, populations in Mississippi. They conducted acute bioassays using fish from an area with no history of insecticide application

TABLE 6-3

Acute Toxicity of HCH to Marine Fishes

Species	Chemical	Concentration (µg/ℓ)	Effect	Reference
Eel				
Anguilla rostrata	lindane	56	96-hour LC_{50}	Eisler, 1970a
Anguilla anguilla	lindane	600-1000	48-hour LC_{50}	Foulquier et al., 1971
Sheepshead minnow *Cyprinoden variegatus*	lindane	104	96-hour LC_{50}	Schimmel et al., 1977
Mummichog *Fundulus heteroditus*	lindane	60	96-hour LC_{50}	Eisler, 1970a
	lindane	20	96-hour LC_{50}	Eisler, 1970b
	lindane	1.6	240-hour LC_{50}	Eisler, 1970b
Longnose killifish *Fundulus similis*	lindane	240	48-hour LC_{50}	Butler, 1963
Striped killifish *Fundulus majalis*	lindane	28	96-hour LC_{50}	Eisler, 1970a
Atlantic silverside *Menidia menidia*	lindane	9	96-hour LC_{50}	Eisler, 1970a
Striped bass *Morone saxatilis*	lindane	7.3	96-hour LC_{50}	Korn and Earnest, 1974
	lindane	400	96-hour LC_{50}	Wellborn, 1971
Pinfish *Lagodon rhomboides*	lindane	30.6	96-hour LC_{50}	Schimmel et al., 1977
	HCH	86.4	96-hour LC_{50}	Schimmel et al., 1977

TABLE 6-3 (cont.)

Species	Chemical	Concentration (μg/ℓ)	Effect	Reference
Bluehead *Thassaloma bifasciatum*	lindane	14	96-hour LC_{50}	Eisler, 1970a
Striped mullet *Mugil cephalus*	lindane	66	96-hour LC_{50}	Eisler, 1970a
	lindane	74	96-hour LC_{50}	Rao and Venugopalan, 1984
		7.4-18.5	inhibition of respiration	Rao and Venugopalan, 1984
White mullet *Mugil curema*	lindane	30	48-hour LC_{50}	Butler, 1963
Northern puffer *Sphaeroides muculatus*	lindane	35	96-hour LC_{50}	Eisler, 1970a

and compared the results with those obtained using fish from a population with a history of exposure to different insecticides. For lindane, they found that the fish from the contaminated area were 42 times more resistant to lindane. The 48-hour LC_{50} values were 3104 and 74 µg/ℓ, respectively. Development of such resistant populations may be the result of selection for resistant individuals over several generations of exposure, or may also be due to induction of detoxification mechanisms in previously-exposed fish.

Table 6-4 contains information about the acute toxicity of lindane to freshwater invertebrates. Cladocerans generally seem to be the most resistant freshwater species, while other crustaceans and insects are among the most sensitive (U.S. EPA, 1980b). The lowest reported acutely toxic concentration was 1 µg/ℓ, the 96-hour LC_{50} for stoneflies, Pteronarcys sp. (Cope, 1965; Snow, 1958). Although lindane is used as an insecticide, the most sensitive invertebrate species are only slightly more sensitive than the most sensitive fishes (U.S. EPA, 1976).

Among saltwater invertebrates, crustaceans were more sensitive to lindane than mollusks or annelids (see Table 6-4). The most sensitive saltwater invertebrate was the pink shrimp, Penaeus duorarum, with a 96-hour LC_{50} of 0.17 µg/ℓ lindane (Schimmel et al., 1977).

Data concerning effects of HCH compounds other than lindane on freshwater and saltwater invertebrates are found in Table 6-5. Lindane appears to be more toxic than other HCH compounds. The species most sensitive to HCH compounds was still the stonefly, Pteronarcys sp., with a 96-hour LC_{50} of <18 µg/ℓ HCH (Johnson and Finley, 1980) and the pink shrimp, with a 96-hour LC_{50} of 0.34 µg/ℓ HCH (Schimmel et al., 1977).

TABLE 6-4

Acute Toxicity of Lindane to Aquatic Invertebrates

Species	Concentration (μg/ℓ)	Effect	Reference
		FRESHWATER SPECIES	
Crustaceans			
Water flea	460	48-hour EC_{50}, immobilization	Sanders and Cope, 1966
Daphnia pulex	420	48-hour EC_{50}, immobilization	Cope, 1966
	1250	LC_{50}	Dive et al., 1980
Daphnia magna	485	LC_{50}	Macek et al., 1976
	1100	24-hour EC_{50}, immobilization	Sanders and Cope, 1966
	516	48-hour LC_{50}, technical grade lindane	Randall et al., 1979
	6442	48-hour LC_{50}, 1% dust	Randall et al., 1979
Daphnia carinata	50	21% mortality, 4 hours	Maity and Saxena, 1979
Cladoceran *Simocephalus serrulatus*	520-880	48-hour EC_{50}, immobilization	Sanders and Cope, 1966
Isopod *Asellus brevicaudus*	10	96-hour LC_{50}	Sanders, 1972
Amphipod	48	96-hour LC_{50}	Sanders, 1969
Gammarus lacustris	120	24-hour LC_{50}	Sanders, 1969
	88	48-hour LC_{50}	Sanders, 1969
Gammarus fasciatus	10-11	96-hour LC_{50}	Sanders, 1972
	39	48-hour LC_{50}	Macek et al., 1976
Gammarus pulex	5.9	96-hour LC_{50}, hard water	Shell Oil Co., 1982;
	13.6	96-hour LC_{50}, soft water	Stephenson, 1983
	34	96-hour LC_{50}	Abel, 1980
Gammarus duebeni	9.6-13.5	96-hour LC_{50}	Inman and Lockwood, 1977
	1.8	decreased hemolymph sodium concentration, 4 days	Inman and Lockwood, 1977
Gammarus sp.	30	24-hour LC_{50}	Bluzat and Seuge, 1979
Ostracod *Cypridopsis* sp.	3.2	96-hour LC_{50}	Johnson and Finley, 1980

TABLE 6-4 (cont.)

Species	Concentration (µg/ℓ)	Effect	Reference
		FRESHWATER SPECIES (cont.)	
Insects			
Midge			
Chironomus tentans	207	LC_{50}	Macek et al., 1976
Chironomus sp.	6	8-hour LC_{50}	McKee and Wolf, 1963
Phantom midge			
Chaoborus sp.	8	24-hour LC_{50}	Bluzat and Seuge, 1979
Mayfly			
Cloeon sp.	92	24-hour LC_{50}	Bluzat and Seuge, 1979
Stonefly			
Pteronarcys californica	12	24-hour LC_{50}	Sanders and Cope, 1968
	4.5	96-hour LC_{50}	Sanders and Cope, 1968
	2	48-hour EC_{50}, immobilization	Cope, 1966
Pteronarcys sp.	1	96-hour LC_{50}	Cope, 1965; Snow, 1958
Orachnids			
Mite			
Hydracha trilobata	50	48-hour LC_{50}	Nair, 1981
Mollusks			
Snail			
Lymnaea sp.	7300	24-hour LC_{50}	Bluzat and Seuge, 1979
Lymnaea stagnalis	2000	96% mortality	Seuge and Bluzat, 1983
	1000	45% mortality	Seuge and Bluzat, 1983
Protozoa			
Colpidium campylum	10,000	Inhibition of culture growth	Dive et al., 1980
		SALTWATER SPECIES	
Crustaceans			
Mysid			
Mysidopsis bahia	6.28	96-hour LC_{50}	Schimmel et al., 1977
Brine shrimp			
Artemia salina	81-210	48-hour LC_{50}	Gaeta et al., 1983

TABLE 6-4 (cont.)

Species	Concentration (µg/ℓ)	Effect	Reference
		SALTWATER SPECIES (cont.)	
Sand shrimp *Crangon septemspinosa*	5.0	96-hour LC_{50}	Eisler, 1969
	14	24-hour LC_{50}	Eisler, 1969
Grass shrimp (unspecified)	62	24-hour LC_{50}	Eisler, 1969
Paloemonetes vulgaris	10.0	96-hour LC_{50}	Eisler, 1969
Palaemonetes pugio	4.44	96-hour LC_{50}	Schimmel et al., 1977
Pink shrimp *Penaeus duorarum*	0.17	96-hour LC_{50}	Schimmel et al., 1977
Korean shrimp *Palaemon macrodactylus*	9.2-12.5	96-hour LC_{50}	U.S. EPA, 1972
Hermit crab *Pagurus longicarpus*	5.0	96-hour LC_{50}	Eisler, 1969
Unspecified	38	96-hour LC_{50}	
Mollusks			
Eastern oyster *Crassostrea virginica*	450	LC_{50}	Butler, 1963
	9100	48-hour LC_{50}, eggs	Davis and Hidu, 1969
Hard clam *Mercenaria mercenaria*	>10,000	48-hour LC_{50}, eggs	Davis and Hidu, 1969
	>10,000	12-day LC_{50}, larvae	Davis and Hidu, 1969
	5000	stimulated growth of larvae	Calabrese, 1971
Annelids			
Polychaete *Neanthes arenaceodentata*	3680	LC_{50}	U.S. EPA, 1980b
Ophryotrocha diadema	>10,000	48-hour LC_{50}	Parker, 1984

TABLE 6-5

Acute Toxicity of Other HCH Isomers to Aquatic Invertebrates

Species	Chemical	Concentration (µg/ℓ)	Effect	Reference
		FRESHWATER SPECIES		
Pond Snail				
Lymnaea stagnalis	α-HCH	1,200	48-hour EC_{50}, immobilization	Canton and Slooff, 1977
Lymnaea sp.	HCH	1,700	100% mortality	McKee and Wolf, 1963
Annelid worms				
Tubifex and *Limnodrilus* sp.	HCH	3,150	96-hour LC_{50}	Whitten and Goodnight, 1966
Copepod				
Cyclops sp.	HCH	125-250	48-hour LC_{50}	Meyer, 1965
Prawn				
Macrobrachium lamarrei	HCH	41.62	96-hour LC_{50}	Shukla and Omkar, 1983
Water Flea				
Daphnia magna	α-HCH	800	EC_{50}, mortality/immobilization	Canton et al., 1975
Daphnia pulex	HCH	680	EC_{50}, immobilization	Johnson and Finley, 1980
Amphipod				
Gammarus lacustris	HCH	78	96-hour LC_{50}	Johnson and Finley, 1980
Stonefly				
Pteronarcys sp.	HCH	<18	96-hour LC_{50}	Johnson and Finley, 1980
		SALTWATER SPECIES		
Pink shrimp				
Penaeus duorarum	HCH	0.34	96-hour LC_{50}	Schimmel et al., 1977
Brown shrimp	Tri-Dust No. 30*	35	24-hour LC_{50}	Chin and Allen, 1957
Penaeus aztecus	Tri-Dust No. 30*	400	24-hour LC_{50}	Chin and Allen, 1957
White shrimp	Tri Dust No. 30*	400	24-hour LC_{50}	Chin and Allen, 1957
Penaeus setiferus	HCH	25	100% mortality, 24 hours	McKee and Wolf, 1963
Brine shrimp				
Artemia salina	α-HCH	500	96-hour LC_{50}	Canton et al., 1978
Polychaete				
Ophryotrocha diadema	α-HCH	>10,000	48-hour LC_{50}	Parker, 1984

*3.0% γ-HCH, 5.1% other HCH isomers, 91.9% inert

6.2. CHRONIC

The available information concerning long-term effects of HCH compounds on freshwater organisms is shown in Table 6-6. No data for saltwater species were available. The lowest concentration reported to cause chronic toxicity was 3.3 μg/ℓ lindane, which was a chronic value for the midge, Chironomus tentans (Macek et al., 1976). Acute toxicity, however, has been reported at lower concentrations in more sensitive species, such as brown trout and stoneflies. Data for these most sensitive species are needed before the chronic toxicity of lindane can be fully evaluated. The available data for other HCH compounds are insufficient to draw any conclusions about their chronic toxicity relative to lindane.

6.3. PLANTS

Table 6-7 contains the available information regarding effects of HCH on aquatic plants. Aquatic plants are less sensitive to HCH compounds than fish and invertebrates (U.S. EPA, 1980b). The lowest concentration reported to cause toxic effects was 80 μg/ℓ HCH, which inhibited growth and DNA synthesis in the blue-green algae, Anabaena aphanizomenoides and Anabaenopsis raciborskii (Das and Singh, 1977). Most reported toxic concentrations for freshwater and marine plant species were ≥1000 (see Table 6-7).

6.4. RESIDUES

There are several studies available concerning the kinetics of uptake and elimination of HCH compounds by aquatic organisms (Table 6-8). Because several of these studies were of short duration, the BCFs that were determined do not represent steady-state values; however, the steady-state BCFs that have been determined indicate that HCH compounds do not bioaccumulate to the same extent as organochlorine compounds such as PCBs and DDT (U.S. EPA, 1980b). BCFs for HCH compounds are generally <1000 (see Table 6-8).

TABLE 6-6

Chronic Toxicity of HCH to Aquatic Organisms

Species	Chemical	Concentration (μg/ℓ)	Effect	Reference
			FISH	
Fathead minnow *Pimephales promelas*	lindane lindane	14.6 15	chronic value chronic value	Macek et al., 1976 Pickering, 1983
Carp *Cyprinus carpio*	HCH	8,000	effect on ovarian recrudescence, 120 days, 50% wettable powder	Kaur and Kirk, 1983
Air-sac catfish *Heteropreustes fossilis*	HCH	200	hematological effects, 30-40 days	Srivastava and Narain, 1982
Trout *Salmo irideus*	lindane	110	histopathological effects in liver and muscle, depressed growth	Boulekbache and Spiess, 1974
Anabantid *Anabas testudineus*	lindane lindane	56 10	100% mortality, 360 days 67% mortality, 360 days	Bakthavathsalam and Reddy, 1981 Bakthavathsalam and Reddy, 1981
			AMPHIBIANS	
Tadpole *Bufo arenarum*	lindane lindane	5,000 1,000	100% mortality, 10-29 days no effect, 10-29 days	Juarez and Guzman, 1984 Juarez and Guzman, 1984
Xenopus laevis	lindane	500	effects on development	Marchal-Segault, 1982; Marchal-Segault and Ramado, 1981
			INVERTEBRATES	
Water flea *Daphnia magna*	lindane α-HCH	14.5 100 50 5	chronic value EC_{50} reproduction, 25 days no effect on mortality/survival, 25 days EC_{10}, reproduction, 25 days	Macek et al., 1976 Canton et al., 1975 Canton et al., 1975 Canton et al., 1975
Amphipod *Gammarus fasciatus*	lindane	6.1	chronic value	Macek et al., 1976
Midge *Chironomus tentans*	lindane	3.3	chronic value	Macek et al., 1976
Pond snail *Lymnaea stagnalis*	α-HCH α-HCH α-HCH lindane	250 230 65 1,000-2,000	EC_{50}, egg production inhibition, 40 days EC_{50}, embryonic development, 40 days reproductive inhibition, 40 days decreased fecundity, growth inhibition	Canton and Slooff, 1977 Canton and Slooff, 1977 Canton and Slooff, 1977 Seuge and Bluzat, 1979, 1983

TABLE 6-7

Effects of HCH on Aquatic Plants

Species	Chemical	Concentration (µg/ℓ)	Effect	Reference
			FRESHWATER SPECIES	
Green alga				
Scenedesmus acutus	HCH	1,000	>20% growth inhibition, 5 days	Krishnakumari, 1977
	α-HCH	500	same as above	Krishnakumari, 1977
	β-HCH	5,000	same as above	Krishnakumari, 1977
	γ-HCH	1,000	same as above	Krishnakumari, 1977
Scenedesmus obliquus	α-HCH	2,000	nontoxic, 21 days	Palmer and Maloney, 1955
	β-HCH	2,000	same as above	Palmer and Maloney, 1955
	γ-HCH	2,000	same as above	Palmer and Maloney, 1955
	γ-HCH	2,000	growth inhibition, 14 days, technical grade	Palmer and Maloney, 1955
	δ-HCH	2,000	growth inhibition, 7 days, technical grade	Palmer and Maloney, 1955
Chlorella variegata	α-HCH	2,000	nontoxic, 21 days	Palmer and Maloney, 1955
	β-HCH	2,000	same as above	Palmer and Maloney, 1955
	γ-HCH	2,000	same as above	Palmer and Maloney, 1955
	δ-HCH	2,000	same as above	Palmer and Maloney, 1955
Chlorella sp.	lindane	300	higher concentrations and irreparable cell damage	Hansen, 1979
Yellow-brown alga				
Gomphonema paruulum	α-HCH	2,000	nontoxic, 21 days	Palmer and Maloney, 1955
	β-HCH	2,000	same as above	Palmer and Maloney, 1955
	γ-HCH	2,000	same as above	Palmer and Maloney, 1955
	γ-HCH	2,000	growth inhibition, 21 days, technical grade	Palmer and Maloney, 1955
	δ-HCH	2,000	no growth, 21 days	Palmer and Maloney, 1955
Nitzschia palea	α-HCH	2,000	nontoxic, 21 days	Palmer and Maloney, 1955
	β-HCH	2,000	same as above	Palmer and Maloney, 1955
	γ-HCH	2,000	same as above	Palmer and Maloney, 1955
	δ-HCH	2,000	growth inhibition, 14 days	Palmer and Maloney, 1955
Blue-green alga				
Cylindrospermum licheniforme	α-HCH	2,000	nontoxic, 21 days	Palmer and Maloney, 1955
	β-HCH	2,000	growth inhibition, 7 days	Palmer and Maloney, 1955
	γ-HCH	2,000	nontoxic, 21 days	Palmer and Maloney, 1955
	δ-HCH	2,000	same as above	Palmer and Maloney, 1955

TABLE 6-7 (cont.)

Species	Chemical	Concentration (µg/ℓ)	Effect	Reference
		FRESHWATER SPECIES (cont.)		
Blue-green alga (cont.)				
Microcystis aeruginosa	α-HCH	2,000	nontoxic, 21 days	Palmer and Maloney, 1955
	β-HCH	2,000	growth inhibition, 7 days	Palmer and Maloney, 1955
	γ-HCH	2,000	nontoxic, 21 days	Palmer and Maloney, 1955
	γ-HCH	2,000	growth inhibition, 21 days, technical grade	Palmer and Maloney, 1955
	δ-HCH	2,000	growth inhibition, 7 days	Palmer and Maloney, 1955
	α-HCH	16% sat	50% kill	Fitzgerald et al., 1952
Nostoc muscorum	HCH	2,000-4,000	decreased growth	Kar and Singh, 1979
Wollea bharadwajae	HCH	2,000-4,000	decreased growth	Kar and Singh, 1979
Anacystis nidulans	lindane	10,000	decreased cell numbers, dry weight, pigment	Kopecek et al., 1975
Anabaena aphanizomenoides	HCH	80	no growth	Das and Singh, 1977
Anabaenopsis raciborskii	HCH	80	same as above	Das and Singh, 1977
		SALTWATER SPECIES		
Phytoplankton (unspecified)	lindane	1,000	28.5% decrease in productivity	Butler, 1963
Alga				
Acetabularia mediterranea	lindane	10,000	inhibition of cell growth	Borghi et al., 1973
Ulva lobata	lindane	650,000	no appreciable inhibition of photosynthesis, 24 hours	Strand et al., 1967
Porphyra perforata	lindane	650,000	same as above	Strand et al., 1967
Paulova lutheri	lindane	7,500	growth inhibition	Escoubet, 1978
Green alga				
Chlamydomonas sp.	α-HCH	1,400	no effects, 48 hours	Canton et al., 1977; U.S. EPA, 1980b
Dunaliella sp.	α-HCH	1,400	no effects on growth, 2-4 days	Canton et al., 1978; U.S. EPA, 1980b
Dunaliella primolecta	lindane	2,500	growth inhibition	Escoubet, 1978
Dunaliella bioculata	lindane	10,000	inhibited DNA synthesis	Jeanne, 1979

TABLE 6-8

HCH Uptake and Elimination by Aquatic Organisms

Species	Chemical	Water Concentration (μg/ℓ)	Duration (days)	BCF	Comments	Reference
FRESHWATER SPECIES						
Fish						
Rainbow trout	lindane	0.05-0.20	242	486	NC	Hamelink and Waybrant, 1976
Salmo gairdneri	lindane	NR	27	319	NC	Ramamoorthy, 1985
Brown trout	α-HCH	500	20	605	NC	Sugiura et al., 1979
Salmo trutta	β-HCH	100	20	658	NC	Sugiura et al., 1979
	γ-HCH	30	20	442	NC	Sugiura et al., 1979
Brook trout	lindane	NR	261	70	Muscle tissue	Macek et al., 1976
Salvelinus fontinalis	lindane	NR	NR	75	NC	Rodgers et al., 1983
Guppy	α-HCH	500	20	588	NC	Sugiura et al., 1979
Poecilia reticulata	β-HCH	100	20	1485	NC	Sugiura et al., 1979
	γ-HCH	30	20	938	NC	Sugiura et al., 1979
	α-HCH	10-50	NR	140	NC	Canton et al., 1975
	α-HCH	800	NR	250	NC	Canton et al., 1975
	α-HCH	10-250	NR	500	Elimination $t_{1/2}$ = 10 hours	Canton et al., 1977
Topmouth gudgeon *Pseudorasbora parva*	lindane	NR	NR	1246	NC	Kanazawa, 1981
Gudgeon	lindane	72	4	15	Muscle, concentration = 1068 ng/g	Marcelle and Thome, 1983
Gobio gobio	lindane	72	4	70	Liver, concentration = 5005 ng/g	Marcelle and Thome, 1983
	lindane	72	4	49	Brain, concentration = 3527 ng/g	Marcelle and Thome, 1983
	lindane	7.5	4	12	Muscle, concentration = 87 ng/g	Marcelle and Thome, 1983
	lindane	7.5	4	34	Liver, concentration = 254 ng/g	Marcelle and Thome, 1983
	lindane	7.5	4	14	Brain, concentration = 108 ng/g	Marcelle and Thome, 1983
	lindane	0.22	4	91	Muscle, concentration = 20 ng/g	Marcelle and Thome, 1983
	lindane	0.22	4	209	Liver, concentration = 46 ng/g	Marcelle and Thome, 1983
	lindane	0.22	4	586	Brain, concentration = 129 ng/g	Marcelle and Thome, 1983
	lindane	1.0	18	1596	Liver, concentration = 1596 ng/g	Marcelle and Thome, 1984
	lindane	1.0	18	759	Brain, concentration = 759 ng/g	Marcelle and Thome, 1984
Fathead minnow	lindane	NR	304	477	Eviscerated	Macek et al., 1976
Pimephales promelas	lindane	NR	NR	1246	NC	Kanazawa, 1982
	lindane	NR	32	182	NC	Veith et al., 1979
	lindane	NR	NR	400	NC	Rodgers et al., 1983
Carp	α-HCH	500	20	330	NC	Sugiura et al., 1979
Cyprinus carpio	β-HCH	100	20	273	NC	Sugiura et al., 1979
	γ-HCH	30	20	281	NC	Sugiura et al., 1979

TABLE 6-8 (cont.)

Species	Chemical	Water Concentration (μg/ℓ)	Duration (days)	BCF	Comments	Reference
					FRESHWATER SPECIES (cont.)	
Fish (cont.)						
Golden orfe	α-HCH	500	20	1216	NC	Sugiura et al., 1979
Leuciscus idus	β-HCH	100	20	973	NC	Sugiura et al., 1979
	γ-HCH	30	20	765	NC	Sugiura et al., 1979
Bluegill	lindane	NR	735	35	Muscle tissue	Macek et al., 1976
Lepomis macrochirus	lindane	NR	NR	30-768	Elimination $t_{1/2}$ = 0.5 days,	Rodgers et al., 1983
	lindane	2.77	NR	420	Elimination $t_{1/2}$ = 1.8 days	Rodgers et al., 1983
	lindane	31.57	NR	211	Elimination $t_{1/2}$ = 1.3 days	Rodgers et al., 1983
	lindane	0.05-0.20	5-81	147-913	NC	Hamelink and Waybrant, 1976
Mosquitofish	lindane	1.67	33	560	NC	Metcalf et al., 1973
Gambusia affinis	lindane	1.4	1-3	166-233	NC	Metcalf et al., 1973
	lindane	NR	NR	560	NC	Rodgers et al., 1983
Cichlid	lindane	500	NR	4.4	Brain, concentration = 2200 ng/g	Herzberg et al., 1980
Sarotherodon galilaeus	lindane	500	NR	0.66-1.0	Gill, concentration = 330-500 ng/g	Herzberg et al., 1980
Invertebrates						
Zooplankton (unspecified)	lindane	0.05-0.20	5-60	170-448	NC	Hamelink and Waybrant, 1976
Waterflea	α-HCH	10-50	NR	60	NC	Canton et al., 1975
Daphnia magna	α-HCH	800	NR	350	NC	Canton et al., 1975
	lindane	1.4	1-3	430-810	NC	Metcalf et al., 1973
Mosquito *Culex* sp.	lindane	1.4	1-3	95-125	NC	Metcalf et al., 1973
Limpet *Ancylus fluviatilis*	lindane	10	1-12	38-59	Compound administration in food and water	Streit, 1979
Snail *Physa* sp.	lindane	1.67	33	456	NC	Metcalf et al., 1973
Clam *Corbicula* sp.	HCH	0.59	18	2240	BCF applies to fat	Hartley and Johnston, 1983
Plants						
Alga *Chlorella pyrenoidosa*	α-HCH	10-800	NR	200	NC	Canton et al., 1975
Chlorella sp.	lindane	NR	1-6	418-1197	NC	Hansen, 1979
Bryophytes	lindane	0.0675	NR	300-350	NC	Frisque et al., 1983

TABLE 6-8 (cont.)

Species	Chemical	Water Concentration (μg/ℓ)	Duration (days)	BCF	Comments	Reference
SALTWATER SPECIES						
Fish						
Pinfish *Lagodon rhomboides*	HCH	1.4-36.0	28	130	Edible tissue	Schimmel et al., 1977
	HCH	1.4-36.0	28	617	Offal tissue	Schimmel et al., 1977
	HCH	32-91	4	482	NC	Schimmel et al., 1977
	lindane	18-31	4	218	NC	Schimmel et al., 1977
Sheepshead minnow *Cyprinodon variegatus*	lindane	42-109	4	490	NC	Schimmel et al., 1977
Invertebrates						
Oyster (unspecified) *Crassostrea virginica*	lindane	50	10	66	NC	Wilson, 1965
	HCH	0.01-0.10	28	218	NC	Schimmel et al., 1977
Mussel *Mytilus edulis*	lindane	NR	NR	154	NC	Geyer et al., 1982
	lindane	0.02	4	240	NC	Zaroogian et al., 1985
	lindane	0.19-1.90	NR	134-156	NC	Ernst, 1977
	mixture of α-HCH and γ-HCH	0.89	NR	106	Elimination $t_{1/2}$ = 19.2 hours	Ernst, 1977
		1.24	NR	100	Elimination $t_{1/2}$ = 22.1 hours	Ernst, 1977
	lindane	0.02-2.98	2-5	74-242	NC	Ernst, 1975
Bivalve mollusks five species	lindane	NR	NR	10-250	NC	Butler, 1967
Grass shrimp *Palaemonetes pugio*	lindane	1-5.5	4	63	NC	Schimmel et al., 1977
Pink shrimp *Penaeus duorarum*	lindane	0.13-0.62	4	84	NC	Schimmel et al., 1977
	HCH	0.19-0.68	4	80		Schimmel et al., 1977
Brine shrimp *Artemis salina*	α-HCH	10-250	NR	60-90	Elimination $t_{1/2}$ = 48-72 hours	Canton et al., 1977
Plants						
Chlamydomonas sp.	α-HCH	NR	NR	310	BCF independent of HCH concentration up to solubility limit	Canton et al., 1977
	α-HCH	NR	NR	2700	BCF calculated on a dry weight basis	Canton et al., 1977
Dunaliella sp.	α-HCH	NR	NR	1500	Same as above	Canton et al., 1977

NR = Not reported; NC = no comment

probably becasue α- and γ-HCH are less lipophilic than most other organochlorines (Rickard and Dulley, 1983). Like other organochlorines, however, the primary site of HCH accumulation is also fat (Sugiura et al., 1979).

Some studies have addressed the relative importance of uptake from water vs. uptake from food in determining levels of HCH accumulation. Hansen (1980) found that lindane uptake from water by Daphnia magna and sticklebacks, Gasterosteus aculeatus, was very rapid, while uptake from food was relatively slow and dependent on the duration of exposure and feeding rate. In a study in which fish, Gobio gobio, were exposed to lindane in water and fed contaminated or uncontaminated diets for 433 hours, uptake from food appeared to be less important than uptake from water (Marcelle and Thome, 1984). Since the difference in lindane content between "contaminated" and "uncontaminated" food, however, was only 2-fold (100 ppm vs. 50 ppb), these results are of questionable validity. In a similar study (Canton et al., 1975), Daphnia magna and rainbow trout, Salmo gairdneri, exposed to α-HCH in food and water, accumulated slightly higher residues than animals exposed to α-HCH in water alone. Rainbow trout receiving α-HCH only in food were found to have concentration ratios (i.e., ppm in fat/ppm in diet) of 0.1-0.7. Great Lakes coho salmon, Oncorhynchus kisutch, fed natural diets containing organochlorine compounds were found to accumulate α-HCH, B-HCH and lindane in proportion to dietary concentrations (Leatherland and Sonstegard, 1982). Concentration ratios in this study ranged from 0.4-0.8 in Lake Ontario fish, the only fish found to have detectable HCH residues in the diet and their tissues.

HCH compounds are generally eliminated more rapidly than other organochlorine compounds such as DDT and dieldrin (Tooby and Durbin, 1975), which could also contribute to the relatively low steady-state BCF values. Elimination half-times for HCH compounds in various species range from <1-3 days (see Table 6-8).

There is relatively little information available concerning metabolism of HCH by aquatic organisms. In a study in which mosquitofish, Gambusia affinis, and snails, Physa sp., were exposed to radiolabeled lindane, 92% of the radioactivity in the fish was in the form of lindane but only 21% in the snails was present as parent compound (Metcalf et al., 1973).

There is a great deal of monitoring information available concerning tissue levels of HCH and other organochlorines in fish. For the purposes of this report, only data from North American waters or data relevant to North American species will be presented (Table 6-9). Whole-body residues for fishes rarely exceed 100 ppb, but HCH concentrations in fat, liver and gall bladder may be considerably higher (Falandysz, 1984; Sugiura et al., 1979); however, since HCH is less lipophilic than other organochlorines, total HCH accumulation in fish tissues may be more dependent on the age of the fish than lipid content (Rickard and Dulley, 1983). In plant species, however, HCH accumulation does seem to depend on lipid content, at least in algae. Canton et al. (1977) found that α-HCH accumulation in two species of algae was proportional to the lipid content of the cells.

Chovelon et al. (1984) reported the results of a monitoring study of freshwater fishes in Alberta, Canada, where lindane was the only organochlorine pesticide widely used; use of other organochlorines (such as DDT, dieldrin, heptachlor epoxide and chlordane) had been discontinued for >10 years. Lindane itself was detected only occasionally in fishes, but α-HCH was found rather frequently. Concentrations of α-HCH in intestinal fat samples were 740 ppb in goldeye, Hiodon alosoides, from the Saskatchewan River, but were ~100 ppb or less in other species and in other areas.

TABLE 6-9

HCH Residues in Tissues of Aquatic Organisms

Species	Location	Chemical	Tissue Concentration (ng/g)	Comments	Reference
		FRESHWATER SPECIES			
Fish					
Sea lamprey *Petromyzon marinus*	northern Lake Huron and Lake Michigan	HCH	6	NC	Kaiser, 1982
Lake trout	Lake Superior	α-HCH	4-40	NC	Konasewich et al., 1978
Salvelinus ramaycush	Lake Superior	lindane	190	detected in 1/20 fish	Parejko et al., 1975
	Lake Superior	HCH	ND	NC	Parejko et al., 1975
	Lake Superior	lindane	50-120	whole fish	Konasewich et al., 1978
	Lake Superior	lindane	30	fillets	Konasewich et al., 1978
	Marquette Fish Hatchery	δ-HCH	40	NC	Parejko and Wu, 1977
Brook trout *Salvelinus fontinalis*	northeastern U.S. lakes	α-HCH	3-19	NC	Haines, 1983
Cisco	Cold Lake, Alberta, Canada	α-HCH	2	muscle	Tsui and McCart, 1981
Coregonus artedii	Cold Lake, Alberta, Canada	α-HCH	98	fat	Tsui and McCart, 1981
Whitefish	Cold Lake, Alberta, Canada	α-HCH	4	muscle	Tsui and McCart, 1981
Coregonus clupeaformis	Cold Lake, Alberta, Canada	α-HCH	71	fat	Tsui and McCart, 1981
	northern Lake Huron and Lake Michigan	HCH	16	whole body	Kaiser, 1982
White sucker	Cold Lake, Alberta, Canada	α-HCH	1	muscle	Tsui and McCart, 1981
Catostomus commerson	Cold Lake, Alberta, Canada	NR	51	fat	Tsui and McCart, 1981
Northern pike	Cold Lake, Alberta, Canada	α-HCH	trace	muscle	Tsui and McCart, 1981
Esox lucius	Cold Lake, Alberta, Canada	α-HCH	84	fat	Tsui and McCart, 1981
Burbot	Lake Huron	lindane	20	average, whole fish	Konasewich et al., 1978
Lota lota	Lake Superior	lindane	50	NC	Konasewich et al., 1978
Channel catfish *Ictalurus punctatus*	Lake Erie	HCH	10-30	NC	Konasewich et al., 1978
Bloater chub *Coregonus hoyi*	Lake Huron	lindane	40	average, whole fish	Konasewich et al., 1978
Slimy sculpin *Cottus cognatus*	Lake Huron	lindane	30	average, whole fish	Konasewich et al., 1978

TABLE 6-9 (cont.)

Species	Location	Chemical	Tissue Concentration (ng/g)	Comments	Reference
		FRESHWATER SPECIES (cont.)			
Emerald shiner *Notropis atherinoides*	Lake Erie	α-HCH	5-6	18 samples	Konasewich et al., 1978
	Lake Erie	β-HCH	ND	18 samples	Konasewich et al., 1978
	Lake Erie	lindane	2-3	18 samples	Konasewich et al., 1978
	Lake Ontario	α-HCH	5	10 samples	Konasewich et al., 1978
	Lake Ontario	β-HCH	1	10 samples	Konasewich et al., 1978
	Lake Ontario	lindane	2-6	10 samples	Konasewich et al., 1978
	Lake Michigan	lindane	1	NC	Konasewich et al., 1978
	Lake Huron	lindane	2	NC	Konasewich et al., 1978
Common shiner *Notropis cornutus*	Lake Huron	lindane	ND	NC	Konasewich et al., 1978
Golden shiner *Notomigonus crysoleucas*	Lake Ontario	lindane	ND	NC	Konasewich et al., 1978
Perch *Perca flavescens*	Lake Erie	HCH	10-30	NC	Konasewich et al., 1978
Herbivorous species	Danube River, Czechoslovokia	lindane	54	species included carp (*C. carpio*)	Sackmauerova et al., 1977
	Danube River, Czechoslovokia	β-HCH	9	NC	Sackmauerova et al., 1977
Carnivorous species	Danube River, Czechoslovokia	lindane	62	species included pike (*Esox lucius*) and pumpkin seed (*Lepomis gibbosus*)	Sackmauerova et al., 1977
	Danube River, Czechoslovokia	β-HCH	23	same as above	Sackmauerova et al., 1977
Several species	Alberta, Canada rivers	α-HCH	0-740	NC	Chovelon et al., 1984
	north-central United States	α-HCH	0-27	NC	Martin and Hartman, 1985
	northeastern Louisiana lakes	HCH, lindane	ND	NC	Niethammer et al., 1984
		SALTWATER SPECIES			
Fish Cod *Gadus morhua*	Baltic Sea	α-HCH	ND-290	liver tissue	Falandysz, 1984
	Baltic Sea	β-HCH	ND-1100	liver tissue	Falandysz, 1984
	Baltic Sea	γ-HCH	ND-400	liver tissue	Falandysz, 1984
	Baltic Sea	δ-HCH	ND	liver tissue	Falandysz, 1984
Atlantic salmon *Salmo salar*	Baltic Sea	α-HCH	9.2	whole body residues	Falandysz, 1982
	Baltic Sea	γ-HCH	370	whole body residues	Falandysz, 1982

TABLE 6-9 (cont.)

Species	Location	Chemical	Tissue Concentration (ng/g)	Comments	Reference
		SALTWATER SPECIES (cont.)			
Invertebrates Zooplankton--Copepods	western North Pacific	HCH	0.26	NC	Tanabe et al., 1984
Myctophid Diaphus suborbitalis	western North Pacific	HCH	2.2	NC	Tanabe et al., 1984
Squid Todarodes pacificus	western North Pacific	HCH	1.1	NC	Tanabe et al., 1984
Mammals Striped dolphin Stenella coeruleoalba	western North Pacific	HCH	77	NC	Tanabe et al., 1984
	Pacific coast of Japan	α-HCH	49-57	blubber	Tanabe et al., 1983
	Pacific coast of Japan	β-HCH	368-434	blubber	Tanabe et al., 1983
	Pacific coast of Japan	γ-HCH	18-22	blubber	Tanabe et al., 1983
	Pacific coast of Japan	α-HCH	0.5-2.5	muscle	Tanabe et al., 1983
	Pacific coast of Japan	β-HCH	3.7-18.6	muscle	Tanabe et al., 1983
	Pacific coast of Japan	γ-HCH	0.2-1.2	muscle	Tanabe et al., 1983
	Pacific coast of Japan	α-HCH	2.8	kidney	Tanabe et al., 1983
	Pacific coast of Japan	β-HCH	57.1	kidney	Tanabe et al., 1983
	Pacific coast of Japan	γ-HCH	1.1	kidney	Tanabe et al., 1983
	Pacific coast of Japan	α-HCH	1.3	liver	Tanabe et al., 1983
	Pacific coast of Japan	β-HCH	55.5	liver	Tanabe et al., 1983
	Pacific coast of Japan	γ-HCH	0.7	brain	Tanabe et al., 1983
	Pacific coast of Japan	α-HCH	16-33	brain	Tanabe et al., 1983
	Pacific coast of Japan	β-HCH	4.7-6.2	brain	Tanabe et al., 1983
	Pacific coast of Japan	γ-HCH	0.6-0.7	brain	Tanabe et al., 1983
	Pacific coast of Japan	HCH	435-513	blubber, total residues	Tanabe et al., 1983
	Pacific coast of Japan	HCH	4.4-22.3	muscle, total residues	Tanabe et al., 1983
	Pacific coast of Japan	HCH	61	liver, total residues	Tanabe et al., 1983
	Pacific coast of Japan	HCH	57.5	kidney	Tanabe et al., 1983
	Pacific coast of Japan	HCH	21-40	brain, total residues	Tanabe et al., 1983
	Pacific coast of Japan	HCH	230-500	concentration in blubber	Tanabe et al., 1983
Pacific white-sided dolphin Lagenorphynehus obliquidence	Pacific coast of Japan	HCH	13,000-15,000	concentration in blubber	Tanabe et al., 1983
Dall's porpoise Phocoenoides dalli	northern Pacific	HCH	870-2200	concentration in blubber	Tanabe et al., 1983
Melon-headed whale Peponocephala electra	Pacific coast of Japan	HCH	40-190	concentration in blubber	Tanabe et al., 1983

NC = No comment; ND = not detected; NR = not reported

Occurrence of the other organochlorine compounds was widespread in all species at low concentrations, despite the fact that they were no longer used. This observation is consistent with the high BCFs and long half-lives of these compounds in fish tissues. Relative to these other organochlorines, HCH does not accumulate appreciably in fish (Chovelan et al., 1984).

These and other monitoring data in Table 6-9 indicate that HCH compounds do not undergo ecological magnification to a great extent. HCH concentrations in carnivorous fish species are comparable to those in herbivorous fish species (Sackmauerova et al., 1977). In addition, laboratory studies with experimental food chains also indicate that HCH is not biomagnified to a great extent (Streit, 1979), especially compared with other organochlorines.

Schmitt et al. (1985) reported the results of a monitoring study of fish tissue residues from 107 freshwater stations in the United States (Table 6-10), and concluded that HCH was relatively short-lived compared with other organochlorines. A decline in tissue concentration and occurrence of detectable HCH residues in fish tissues were observed from 1976-1981. In the 1980-1981 sampling period, whole-body lindane residues were >10 ng/g only at one station in Hawaii, where levels were 20-30 ng/g. Tissue concentrations of α-HCH were generally higher than lindane, and the highest concentrations (30-40 ng/g) were found in fish from stations in the southwest and midwest.

In a monitoring study of marine species, Tanabe et al. (1984) found that the primary form of HCH in seawater, zooplankton, squid, Todarodes pacificus, and myctophids, Diaphys suborbitalis, was α-HCH. In a marine mammal, the striped dolphin, Stenello coeruleoalba, >50% of the total HCH concentration was β-HCH (Tanabe et al., 1983, 1984).

TABLE 6-10

Maximum and Mean Wet Weight and Lipid Weight Residue Concentrations of α-HCH and Lindane from Whole Fish Samples Collected from 107 Stations in the United States*

Chemical	Maximum Concentrations (ng/g)									Mean Concentrations (ng/g)					
	1976-1977			1978-1979			1980-1981			Wet Weight			Lipid Weight		
	W	L	%	W	L	%	W	L	%	1976-1977	1977-1978	1980-1981	1976-1977	1977-1978	1980-1981
α-HCH	300	6300	89.6	40	2000	53.7	40	900	54.2	20	<10	<10	300	100	100
Lindane	280	9300	31.1	20	600	8.3	30	400	15.9	10	<10	<10	100	<100	<100

*Source: Schmitt et al., 1985

W = Wet weight; L = lipid weight; % = percentage of stations where detectable residues were found

Tanabe et al. (1983, 1984) presented information concerning HCH residues in marine mammals of the Pacific Ocean. Blubber of these species contained the highest reported HCH residues. The highest concentration, 13,000-15,000 ng/g, was found in blubber of the Pacific white-sided dolphin, Lagenorhynchus obliquidence, which inhabits northern temperate waters that contain high levels of organochlorines relative to other areas. Species from Arctic and Antarctic waters contained lower HCH residues. Tanabe et al. (1983) concluded that because of their long lifespans and their position as top-level carnivores, marine mammals are likely to accumulate high levels of organochlorines including HCH.

6.5. SUMMARY

There is a large volume of information available concerning effects of HCH on aquatic organisms. Lindane (γ-HCH) is generally more toxic to freshwater and saltwater fish and invertebrates than other HCH isomers or mixtures (U.S. EPA, 1980b). The lowest reported acutely toxic concentrations for freshwater species were 1.7 $\mu g/\ell$ lindane, which was a 96-hour LC_{50} for brown trout (Johnson and Finley, 1980) and 1 $\mu g/\ell$ lindane, which was a 96-hour LC_{50} for stoneflies (Cope, 1965. Snow, 1958). The lowest reported acutely toxic lindane concentrations for marine fish and invertebrates, respectively, were 7.3 $\mu g/\ell$, a 96-hour LC_{50} for striped bass (Korn and Earnest, 1974), and 0.17 $\mu g/\ell$, a 96-hour LC_{50} for pink shrimp (Schimmel et al., 1977). Among the freshwater fishes, salmonids appeared to be more sensitive than other species. Crustaceans other than cladocerans were generally the most sensitive invertebrate species both in freshwater and saltwater (U.S. EPA, 1980b). Fish and invertebrates appeared to be about equally sensitive to HCH.

In chronic toxicity studies, no adverse effects were reported at concentrations lower than the acutely toxic levels for the most sensitive species; however, chronic toxicity data for the most acutely sensitive species were generally unavailable.

The available information indicated that aquatic plants were much less sensitive to HCH than fish or invertebrates.

HCH accumulates in aquatic biota primarily in fatty tissue; however, HCH is less lipophilic and less persistent than other organochlorines and therefore is not bioaccumulated or biomagnified to a great extent.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The existing guidelines for human exposure to HCH from ambient water are based on cancer data. These values, summarized in Table 7-1, were derived by the U.S. EPA (1980a, 1982b). The q_1^* for γ-HCH (lindane) reported in Table 7-1 is also reported in a Health Effects Assessment (U.S. EPA, 1984a) and a Drinking Water Criteria Document (U.S. EPA, 1985a). Values were not available for either δ- or ε-HCH.

In addition, an RfD for oral exposure to γ-HCH has been estimated and verified by the U.S. EPA (1985a, 1986a). This ADI of 0.023 mg/day (0.0003 mg/kg/day) for a 70 kg human was based on a rat subchronic oral NOAEL of 0.33 mg/day (Research and Consulting Co., Ltd., 1983) and an uncertainty factor of 1000.

OSHA (1985) and ACGIH (1985-1986) recommend a TWA of 0.5 mg/m³ for lindane (γ-HCH) and indicate that dermal exposure may be substantial.

7.2. AQUATIC

U.S. EPA (1980b) derived an ambient water quality criterion for lindane for the protection of aquatic life. For the protection of freshwater species, the concentration of lindane should be ≤0.8 μg/ℓ as a 24-hour average and should be ≤2.0 μg/ℓ at any time. For saltwater species, the lindane concentrations should be ≤0.16 μg/ℓ at any time. No criteria were derived for other HCH isomers or BHC, but U.S. EPA (1980b) noted that acute toxicity to freshwater and saltwater species occurred at concentrations as low as 100 and 0.34 μg/ℓ HCH, respectively, and would occur at lower concentrations in species more sensitive than those tested.

U.S. EPA (1976) recommended criteria of 0.01 μg/ℓ to protect freshwater organisms and 0.04 μg/ℓ to protect saltwater organisms.

TABLE 7-1

Ambient Water Quality Criteria for the Protection of Human Health[a]

Compound	q_1^{*a} (mg/kg/day)$^{-1}$	Ambient Water Quality Criterion[a,b] (ng/ℓ)	Basis	Reference
α-HCH	11.12	22	Increased incidence of liver nodules in male dd mice fed 250 and 500 ppm for 24 weeks	Nagasaki et al., 1972a
β-HCH	1.84	134	Increased incidence of liver neoplasms in male CF1 mice fed 200 ppm for 110 weeks[b]	Thorpe and Walker, 1973
γ-HCH	1.326	186	Increased incidence of liver neoplasms in male CF1 mice fed 400 ppm for 110 weeks	Thorpe and Walker, 1973
T-HCH	4.75	52	Increased incidence of liver neoplasms in male dd mice fed 6, 66 and 660 ppm for 24 weeks	Nagasaki et al., 1972b

[a] Source: U.S. EPA, 1980a, 1982b

[b] Water concentration calculated to keep the individual lifetime cancer risk below 10^{-5}. Assumes daily consumption of 2 ℓ of water and 6.5 g of fish and shellfish.

8. RISK ASSESSMENT

8.1. α-HCH

Dietary α-HCH has been shown to cause an increased incidence of liver tumors in five strains of mice (Ito et al., 1973a,b, 1976; Nagasaki et al., 1972a, 1975; Hanada et al., 1973; Goto et al., 1972) and in Wistar rats (Ito et al., 1975; Schulte-Hermann and Parzefall, 1981). The teratogenic and reproductive effects of α-HCH have not been investigated. Nonneoplastic hepatic changes have occurred in rats and mice fed α-HCH (Shulte-Hermann and Parzefall, 1981; Ito et al., 1973a,b, 1975, 1976; Fitzhugh et al., 1950).

According to EPA criteria, there is sufficient evidence to conclude that α-HCH is carcinogenic to animals. A past assessment for α-HCH (U.S. EPA, 1982b) derived a q_1^* for humans of 11.1 $(mg/kg/day)^{-1}$ on the basis of an increased incidence of liver neoplasms in male DDY mice fed 250 and 500 ppm α-HCH in the diet for 24 weeks (Nagasaki et al., 1972a). The data from the past assessment of the U.S. EPA (1982b) to estimate the α-HCH q_1^* are presented in Table 8-1.

There are, however, a number of problems with these two data sets. Nagasaki et al. (1972a) reported only the incidences of macroscopic liver nodules in groups of mice fed 0, 100 ppm (13 mg/kg/day), 250 ppm (37.5 mg/kg/day) or 500 ppm (65.0 mg/kg/day) of α-HCH in the diet. Although Nagasaki et al. (1972a) mentioned that histological examination revealed benign and malignant hepatomas in the livers of mice fed 250 or 500 ppm α-HCH, they did not report incidences of histologically verified tumors and did not indicate whether the livers of mice fed 0 or 100 ppm of α-HCH were examined histologically. Hence, the incidence data used in the past by U.S. EPA (1982b) to estimate a q_1^* is for grossly observable liver nodules

TABLE 8-1

Summary of Pertinent Data for q_1^* for α-HCH[a]

The water quality criterion for α-HCH is derived from the oncogenic effects observed in the livers of male dd mice fed 0, 250 or 500 ppm α-HCH in the diet for 24 weeks. These dietary levels correspond to TWA doses of 0, 37.5 or 65 mg/kg/day, respectively. The criterion was calculated from the following parameters without the 13 mg/kg/day dose:

Dose (mg/kg/day)	Incidence of Grossly Observable Liver Nodules[b] (No. responding/No. tested)
0	0/20
13.0	0/20
37.5	9/20
65.0	20/20

le = 24 weeks   w = 0.030 kg
LE = 24 weeks
L = 90 weeks

With these parameters the carcinogenic potency factor for humans, q_1^*, is 11.12 $(mg/kg/day)^{-1}$[c].

---

[a] Source: Nagasaki et al., 1972a

[b] These tumors are not hepatocellular carcinomas nor do they appear to be hepatomas, but rather are swellings leading "nodules."

[c] When dose-response data for the lowest dosage group (dose = 13 mg/kg/day, incidence = 0/20) is included in the analysis, the q_1^* for humans is 3.03 $(mg/kg/day)^{-1}$ for L = 90 weeks or 4.68 $(mg/kg/day)^{-1}$ for L = 104 weeks:

Animal $q_1^* = 4.335761 \times 10^{-3}$ $(mg/kg/day)^{-1}$

Human $q_1^* = 3.03$ $(mg/kg/day)^{-1}$ = animal $q_1^* \times (70/0.03)^{1/3} \times (90/24)^3$

Human $q_1^* = 4.68$ $(mg/kg/day)^{-1}$ = animal $q_1^* \times (70/0.03)^{1/3} \times (104/24)^3$

only, and omits the incidence in the lowest dosage group. If the dose-response for this previously omitted group (dose = 13 mg/kg/day; incidence = 0/20) is included in the q_1* derivation, the resulting q_1* is 3.03 $(mg/kg/day)^{-1}$ with a mouse lifespan of 90 weeks, or 4.68 $(mg/kg/day)^{-1}$ when the lifespan of the mice is assumed to be 104 weeks, a time correction consistent with current methodology (U.S. EPA, 1985b).

Ito et al. (1973a) performed a similar study on male dd mice using the same dietary levels and duration (but a larger 250 ppm group) and obtained similar results. The Ito et al. (1973a) study, however, provides combined incidence data for histologically confirmed liver tumors (nodular hyperplasia and hepatocellular carcinoma). The data of Ito et al. (1973a), summarized in Table 8-2, yield a q_1* for humans of 6.3 $(mg/kg/day)^{-1}$ when the lifespan of the mice is assumed to be 104 weeks, consistent with current methodology (U.S. EPA, 1985b). The q_1* of 6.3 $(mg/kg/day)^{-1}$ is recommended as the best estimate of the carcinogenic potency of α-HCH. The corresponding water levels associated with maximum increased lifetime cancer risks for humans of 10^{-5}, 10^{-6} and 10^{-7} are 5.52×10^{-5}, 5.52×10^{-6} and 5.52×10^{-7}, respectively. The Ito estimate [6.34 $(mg/kg/day)^{-1}$] of cancer potency does not vary greatly from the above-reviewed Nagasaki estimate [4.6 $(mg/kg/day)^{-1}$].

A q_1* was also derived from the only available oral study that involved chronic administration (i.e., >24-32 weeks of the other studies) of α-HCH and that reported combined incidences of benign and malignant liver tumors (Section 9.2.1.). In the 26-month study by Schulte-Hermann and Parzefall (1981), the combined incidence of hepatic neoplastic nodules and hepatocellular carcinomas in Wistar rats was 6/6 in female Wistar rats fed ~20 mg/kg/day of α-HCH for 20-26 months vs. 1/6 in controls (p=0.008,

TABLE 8-2

Derivation of a q_1^* for α-HCH

Reference: Ito et al., 1973a

Species/strain/sex: mouse/dd/male

Route/vehicle: oral/diet

Tumor site and type: liver, nodular hyperplasia[a] and hepatocellular carcinoma

le = 24 weeks

LE = 24 weeks

L = 104 weeks

bw = 0.03 kg (assumed)

Exposure (ppm)	Transformed Dose[b] (mg/kg/day)	Incidence
0	0	0/20
100	13.0	0/20
250	37.5	10/38
500	65.0	20/20

---

[a] The hyperplasia was considered to be a precursor to tumor development in this experiment and as such was added into the tumor counts.

[b] Dose was transformed by multiplying dietary ppm by a food factor of 0.13 to obtain doses in mg/kg/day.

Animal $q_1^* = 5.870060 \times 10^{-3}$ $(mg/kg/day)^{-1}$

Human $q_1^* = 6.34$ $(mg/kg/day)^{-1}$ = animal $q_1^* \times (70/0.03)^{1/3} \times (104/24)^3$

Fisher Exact test). Because Global 82 will not converge when there are only two groups (control and exposed) with 100% response in one of the groups, it was necessary to reduce the incidence to a value <100% and to adjust the dose proportionally (Table 8-3). The adjusted data yield a q_1* for humans of 1.3 $(mg/kg/day)^{-1}$, which is only somewhat smaller, but of the same order of magnitude as the q_1* derived for α-HCH from the much shorter (24-week) study by Ito et al. (1973a). Such relative agreement may be fortuitous but does suggest that the true upper limit estimate is likely to lie in the 1.33-6.38 $(mg/kg/day)^{-1}$ range.

8.2. β-HCH

Dietary β-HCH has been shown to cause an increased incidence of liver tumors in CF1 mice (Thorpe and Walker, 1973). Tumors were not increased in dd mice (Ito et al., 1973a,b; Hanada et al., 1973; Nagasaki et al., 1972a) or Wistar rats (Ito et al., 1975; Fitzhugh et al., 1950). The Thorpe and Walker (1973) study is the only positive cancer study for β-HCH. As previously discussed (see Section 5.1.1.), an additional report (Goto et al., 1972) indicates that mice fed 600 ppm of β-HCH had no grossly observable liver nodules but had histological evidence of benign hepatomas at an unspecified incidence, which is considered to be marginal evidence at best.

The reproductive and teratogenic effects of β-HCH have not been investigated. Ito et al. (1973a,b, 1975) found neither nonneoplastic nor neoplastic histological changes in the livers of mice and rats in studies that were designed to investigate hepatic carcinogenic response; however, increases in absolute and relative liver weight were observed at dietary concentrations ≥250 ppm. Fitzhugh et al. (1950) observed increased liver weight accompanied by histological changes in rats fed ≥100 ppm β-HCH; increased relative liver weight was the only effect observed at 10 ppm.

TABLE 8-3

Derivation of a q_1^* for α-HCH

Reference: Schulte-Hermann and Parzefall, 1981

Species/strain/sex: rat/Wistar/female

Route/vehicle: oral/diet

Tumor site and type: liver, neoplastic nodules and hepatocellular carcinomas

le = 20-26 months

LE = 20-26 months[a]

L = 20-26 months[a]

bw = 0.35 kg (assumed)

Exposure (mg/kg/day)	Transformed Dose (mg/kg/day)	Incidence
0	0	1/6
20	16.67 (20)[b]	5/6 (6/6)[b]

---

[a] Assumed; data are unclear (Section 9.2.1.)

[b] Since GLOBAL 82 will not converge when there are only two groups and when one of the groups has 100% response, it was necessary to reduce the incidence from 6/6 to 5/6 and to adjust the dose to 5/6 of the original value (5/6x20 = 16.67).

Animal $q_1^* = 2.27421068\times10^{-1}$ (mg/kg/day)$^{-1}$

Human $q_1^* = 1.33$ (mg/kg/day)$^{-1}$ = animal $q_1^* \times (70/0.35)^{1/3}$

Early mortality was also observed among rats fed 800 ppm. Although no tumors were observed in this study, not all of the rats started on the test were examined histologically (no criterion for selection was given). No other chronic effects were reported.

According to EPA criteria, there is limited evidence that β-HCH is carcinogenic to mice. This limitation is based in part on only one positive mouse study (CFI strain), a marginal mouse study (ICR-JCL strain), four negative mouse tests in 24-week studies (all dd strain mice), and two negative long duration studies using Wistar rats. U.S. EPA (1980a) has previously derived a q_1^* for humans of 1.84 $(mg/kg/day)^{-1}$ based on the increased combined incidence of hepatic hyperplastic nodules and hepatocellular carcinomas in male CF1 mice fed 200 ppm β-HCH in the diet for 110 weeks (Thorpe and Walker, 1973). These data are summarized and quantified in Table 8-4 and are recommended to best represent any putative carcinogenic potency of β-HCH, keeping in mind the limitations of the weight of evidence. No additional studies of the carcinogenicity of β-HCH have been published since the U.S. EPA (1982a) document. The corresponding water levels associated with maximum increased lifetime cancer risks for humans of 10^{-5}, 10^{-6} and 10^{-7} are 1.90×10^{-4}, 1.90×10^{-5} and 1.90×10^{-6} mg/ℓ, respectively.

8.3. γ-HCH (Lindane)

Dietary γ-HCH was shown to cause an increased incidence of liver tumors in male CF1 mice fed 400 ppm for 110 weeks (Thorpe and Walker, 1973). Marginal cancer responses were also observed in three other studies: 1) in male dd mice fed 600 ppm for 32 weeks and examined 5-6 weeks after treatment (Hanada et al., 1973); 2) in male ICR-JCL mice fed 600 ppm for 26 weeks (Goto et al., 1972); and 3) in B6C3F1 mice dosed up to 160 ppm, when

TABLE 8-4

Summary of Pertinent Data for q_1* for β-HCH[a]

The water quality criterion for β-HCH is derived from the oncogenic effects observed in the livers of male CF1 mice fed 200 ppm β-HCH in the diet for 110 weeks (Thorpe and Walker, 1973). A TWA dose of 26.0 mg/kg/day was derived from this exposure. The criterion is calculated from the following parameters:

Dose (mg/kg/day)	Incidence[b] (no. responding/no. tested)
0	11/45
26.0	22/24

le = 110 weeks w = 0.030 kg
LE = 110 weeks
L = 110 weeks

With these parameters the carcinogenic potency factor for humans, q_1*, is 1.84 $(mg/kg/day)^{-1}$.

---

[a] Source: U.S. EPA, 1982a

[b] Combined incidence of hyperplastic nodules and hepatocellular carcinomas, subsequent to the finding of the first tumor in any tissue in each group of mice (Section 9.2.2.)

compared with pooled controls at 90 weeks. On the other hand, no liver tumors were observed in dd mice fed up to 500 ppm for 24 weeks (Ito et al., 1973a,b; Nagasaki et al., 1972a) or in Wistar rats fed 500 ppm for up to 48 weeks (Ito et al., 1975). Significant compound-related development of tumors of any type was not observed in NMRI mice (Herbst et al., 1975; Weisse and Herbst, 1977), B6C3F1 mice (NCI, 1977), Osborne-Mendel rats (NCI, 1977) or Wistar rats (Fitzhugh et al., 1950). The study conducted by NCI (1977) has been criticized for poor survival of rats, changes in dosing regimen and the possibility that male rats did not receive MTDs (IARC, 1979). The negative findings of Fitzhugh et al. (1950) are also inconclusive since only small numbers of animals were examined histologically. The negative findings of Ito et al. (1973a,b), Nagasaki et al. (1972a) and Ito et al. (1975) is likely to be attributable to small numbers of animals and short duration.

Orally-administered γ-HCH was not found to be teratogenic or fetotoxic in Wistar rats (Khera et al., 1979), CD rats (Palmer et al., 1978a), CFY rats (Palmer et al., 1978b), New Zealand White rabbits (Palmer et al., 1978b) or CD-1 mice (Chernoff and Kavlock, 1983; Gray and Kavlock, 1984). In contrast, a study by Dzierzawski (1977) reported increased numbers of resorbed fetuses in hamsters (40 mg/kg on day 9 of gestation), rabbits (40 or 60 mg/kg on day 9 of gestation) or rats (40, 50 or 100 mg/kg on various days of gestation). Maternal toxicity, if any, was not reported. These doses are higher than any of those tested in the negative result studies, though Chernoff and Kavlock (1983) reported that 25 mg/kg/day was the maximum dose that was not toxic to maternal CD-1 mice.

Palmer et al. (1978a) observed no adverse effects on reproduction in three generations of CD rats fed up to 100 ppm γ-HCH in the diet. Dikshith and Datta (1977) and Dikshith et al. (1978), however, observed testicular atrophy in ITRC rats gavaged with 17.6 mg γ-HCH/kg in peanut oil for 90 days, suggesting that γ-HCH might have adverse effects upon reproduction.

Long-term oral studies have associated exposure to HCH with nonneoplastic liver changes (Dikshith et al., 1978; Fitzhugh et al., 1950; Research and Consulting Co., Ltd., 1983; Oesch et al., 1982; Ito et al., 1973a, Rivett et al., 1978), kidney changes (Fitzhugh et al., 1950; Research and Consulting Co., Ltd., 1983), hematological effects (Earl et al., 1970; Morgan et al., 1980) and neurotoxicity (Fitzhugh et al., 1950; Czegledi-Janko and Avar, 1970). Short-term studies suggest that γ-HCH may cause immunosupression (Dewan et al., 1980; Desi et al., 1978).

According to EPA criteria, there is sufficient limited evidence that γ-HCH is carcinogenic to animals. U.S. EPA (1980a) has in the past derived a q_1^* of 1.3 $(mg/kg/day)^{-1}$ based on the increased combined incidence of hepatic hyperplastic nodules and hepatocellular carcinomas in male CF1 mice fed 400 ppm γ-HCH in the diet for 110 weeks (Thorpe and Walker, 1973). These data are summarized in Table 8-5. There are no more recent data available that could provide a better estimate of carcinogenic potency for γ-HCH. Corresponding water levels associated with maximum increased lifetime cancer risks for humans of 10^{-5}, 10^{-6} and 10^{-7} are 2.64×10^{-4}, 2.64×10^{-5} and 2.64×10^{-6} mg/ℓ, respectively.

TABLE 8-5

Summary of Pertinent Data for q_1* for γ-HCH[a]

The water quality criterion for γ-HCH is derived from the oncogenic effects observed in the livers of male CF1 mice fed 400 ppm γ-HCH in the diet (Thorpe and Walker, 1973). The TWA dose of 52 mg/kg/day was given in the feed for 110 weeks. The criterion is calculated from the following parameters:

Dose (mg/kg/day)	Incidence[b] (no. responding/no. tested)
0	11/45
52	27/28

le = 770 days   w = 0.030 kg
LE = 770 days
L = 770 days

With these parameters, the q_1* for humans is 1.326 $(\text{mg/kg/day})^{-1}$.

---

[a] Source: U.S. EPA, 1980a

[b] Combined incidence of hyperplastic nodules and hepatocellular carcinomas, subsequent to the finding of the first tumor in any tissue in each group of mice (see Section 9.2.3.)

8.4. δ-HCH

Dietary δ-HCH did not cause neoplastic or nonneoplastic changes in the livers of male dd mice (Ito et al., 1973a; Nagasaki et al., 1972a) or male Wistar rats (Ito et al., 1975). These studies used small numbers of animals, were conducted for only 24 weeks and examined only liver effects. Goto et al. (1972) reported that a mixture of δ- and ε-HCH caused an increased incidence of benign and malignant hepatomas in ICR-JCL mice after 26 weeks of dietary administration, but the individual isomers were not tested in this study. This constitutes limited animal evidence and thus is in EPA Group C. Other pertinent data regarding the teratogenic, reproductive or chronic effects of δ-HCH could not be located in the available literature as cited in the Appendix.

8.5. ε-HCH

Goto et al. (1972) reported that a mixture of δ- and ε-HCH caused an increased incidence of benign and malignant hepatomas in ICR-JCL mice after 26 weeks of dietary administration, but the individual isomers were not tested in this study. This constitutes limited animal evidence and thus is in EPA Group C. Other pertinent data regarding the health effects associated with exposure to ε-HCH could not be located in the available literature as cited in the Appendix.

8.6. T-HCH

T-HCH has been shown to cause increased incidences of liver neoplasms in four strains of mice (Hanada et al., 1973; Goto et al., 1972; Kashyap et al., 1979; Nigam et al., 1984a; Bhatt et al., 1981; Munir et al., 1983; Nagasaki et al., 1971, 1972b; Nagasaki, 1973; Munir and Bhide, 1984) but not in Wistar rats (Munir et al., 1983) or Syrian golden hamsters (Munir et al., 1983).

The teratogenic effects of T-HCH have not been investigated. Nigam et al. (1979) and Shivanandappa and Krishnakamuri (1981, 1983) have shown that orally-administered T-HCH causes testicular atrophy in rats and mice (≥800 ppm, rats; 500 ppm, mice).

Long-term oral administration of T-HCH has been shown to cause adverse effects on the liver (Fitzhugh et al., 1950; Barros and Saliba, 1978; Barros et al., 1982; Shivanandappa and Krishnakamuri, 1981; Nigam et al., 1982, 1984a,b; Munir and Bhide, 1984), kidney (Fitzhugh et al., 1950, Barros and Saliba, 1978; Barros et al., 1982; Shivanandappa and Krishnakamuri, 1981), adrenal cortex (Shivanandappa and Krishnakamuri, 1981; Shivanandappa et al., 1982) and CNS (Shivanandappa and Krishnakamuri, 1981; Kashyap et al., 1979). Kashyap et al. (1979) also reported that long-term oral exposure to T-HCH was associated with increased corneal opacity.

According to EPA criteria, there is sufficient evidence that T-HCH is carcinogenic in animals (Group B2). U.S. EPA (1982b) in the past derived a q_1^* of 4.7 $(mg/kg/day)^{-1}$ based on increased combined incidences of hepatic hyperplastic nodules and hepatomas in male dd mice fed 6.6, 66 and 660 ppm T-HCH for 24 weeks (Nagasaki et al., 1972b) (Table 8-6). However, this is not a malignant tumor endpoint, but it is assumed that the nodules would progress to hepatomas and the hepatomas to carcinomas. In estimating this q_1^*, the U.S. EPA (1982b) assumed the lifespan of the mice was 90 weeks. If the lifespan is assumed to be 104 weeks, consistent with current methodology (U.S. EPA, 1985b), the q_1^* for humans is 7.3 $(mg/kg/day)^{-1}$.

TABLE 8-6

Summary of Pertinent Data for q_1^* for T-HCH[a]

The water quality criterion for T-HCH is derived from the oncogenic effects observed in the livers of male dd mice fed 6.6, 66 or 660 ppm T-HCH in the diet for 24 weeks (Nagasaki et al., 1972b). These dietary levels correspond to TWA doses of 0.858, 8.58 or 85.8 mg/kg/day, respectively. The criterion is calculated from the following parameters:

Dose (mg/kg/day)	Incidence[b] (no. responding/no. tested)
0	0/14
0.858	0/20
8.58	0/20
85.8	20/20

le = 24 weeks w = 0.036 kg
LE = 24 weeks
L = 90 weeks (104 weeks)[c]

With these parameters the carcinogenic potency factor for humans, q_1^*, is 4.75 $(mg/kg/day)^{-1}$[c].

---

[a] Source: U.S. EPA, 1982b

[b] Combined incidence of hyperplastic nodules and hepatomas

[c] Use of an assumed lifespan (L) of 104 weeks, which is consistent with current methodology (U.S. EPA, 1986b), gives a q_1^* for humans of 7.35 $(mg/kg/day)^{-1}$ as follows:

Animal $q_1^* = 7.232384 \times 10^{-3}$

Human $q_1^* = 7.35\ (mg/kg/day)^{-1} = \text{animal}\ q_1^* \times (70/0.036)^{1/3} \times (104/24)^3$

There are additional data available from which a q_1^* can be derived. Munir et al. (1983) observed a dose- and duration-related increase in the combined incidence of hepatic benign nodules and hepatocellular carcinomas in male Swiss mice fed 0, 125, 250 or 500 ppm T-HCH from 8-10 weeks of age until either 8-11, 12-14, 15-17 or 18-22 months of age. Once 100% response was observed at a particular level of treatment, mice were no longer examined at that level of treatment. Instead, data from age groups that include one group with 100% response and response data for more than one dosage (12-14 months; 15-17 months) were used to calculate q_1^* values. These data are summarized in Tables 8-7 and 8-8. (Detailed incidence data for all groups are provided in Section 9.2.6.). A human q_1^* of 1.17 $(mg/kg/day)^{-1}$ was obtained from data on mice that were killed at 12-14 months of age; a human q_1^* of 1.76 $(mg/kg/day)^{-1}$ was obtained from data on mice that were killed at 15-17 months of age. These values are similar to, but somewhat lower than, the q_1^* values based on the 24-week study of Nagasaki et al. (1972b).

The data of Munir et al. (1983) for mice killed at 15-17 months of age are recommended as the best basis for a q_1^* [1.76 $(mg/kg/day)^{-1}$]. This q_1^* is considered to be the best estimate because treatment was for a greater proportion of the animals' lifespan and was at a dosage that defined dose-response relationships more clearly than do the data of Nagasaki et al. (1972b). Water levels corresponding to the recommended q_1^* of 1.76 $(mg/kg/day)^{-1}$ and associated with a maximum increased lifetime cancer risk for humans of 10^{-5}, 10^{-6} and 10^{-7} are 1.99×10^{-4}, 1.99×10^{-5} and 1.99×10^{-6} mg/ℓ, respectively.

TABLE 8-7

Derivation of a q_1^* for T-HCH

Reference: Munir et al., 1983

Species/strain/sex: mouse/Swiss/male

Route/vehicle: oral/diet

Tumor site and type: liver, benign nodules and hepatocellular carcinomas

le = LE = from 8-10 weeks of age to 12-14 months of age (≈12 months)

L = 104 weeks (24 months)

bw = 0.03 kg (assumed)

Exposure (ppm)	Transformed Dose[a] (mg/kg/day)	Incidence
0	0	0/16[b]
125	16.25	0/10
250	32.50	9/12
500	65.00	10/10

---

[a] Dose was transformed by multiplying concentration in ppm by a food factor of 0.13.

[b] Control data are from a similar experiment in male Swiss mice performed in the same laboratory and reported in the same paper.

Animal $q_1^* = 1.1033241 \times 10^{-2}$ (mg/kg/day)$^{-1}$

Human $q_1^* = 1.17$ (mg/kg/day)$^{-1}$ = animal $q_1^* \times (70/0.03)^{1/3} \times (24/12)^3$

TABLE 8-8

Derivation of the q_1^* for T-HCH Recommended as the Best Estimate of Cancer Potency for T-HCH

Reference: Munir et al., 1983

Species/strain/sex: mouse/Swiss/male

Route/vehicle: oral/diet

Tumor site and type: liver, benign nodules and hepatocellular carcinomas

le = LE = from 8-10 weeks of age to 15-17 months of age (~15 months)

L = 104 weeks (24 months)

bw = 0.03 kg (assumed)

Exposure (ppm)	Transformed Dose[a] (mg/kg/day)	Incidence
0	0	2/22[c]
125	16.25	8/20
250	32.50	12/12

---

[a] Animals at 500 ppm were not examined at this age since 100% response was observed at this level among mice that were 12-14 months of age.

[b] Dose was transformed by multiplying concentration in ppm by a food factor of 0.13.

[c] Control data are from a similar experiment in male Swiss mice performed in the same laboratory and reported in the same paper. The controls, however, were killed at 15-20 months of age.

Animal $q_1^* = 3.2323128 \times 10^{-2}$ (mg/kg/day)$^{-1}$

Human $q_1^* = 1.76$ (mg/kg/day)$^{-1}$ = animal $q_1^* \times (70/0.03)^{1/3} \times (24/15)^3$

9. REPORTABLE QUANTITY

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

A large body of evidence indicates that the nonneoplastic changes in the liver associated with dietary exposure to isomers of HCH or T-HCH are associated with neoplastic development. A clear progression of hepatic changes that ultimately lead to the development of malignant tumors has been observed at gross, histological and ultrastructural levels of examination. These changes, proportional to dose and duration of treatment, are reversible only at the very earliest stages before development of nodular hyperplasia; the transition from reversible to irreversible change is not well-defined (Ito et al., 1975, 1976; Schulte-Hermann and Parzefall, 1981; Munir et al., 1983; Munir and Bhide, 1984; Nigam et al., 1982, 1984a; Sugihara et al., 1975). Therefore, preneoplastic hepatic changes were not considered in the derivation of RQs for chronic toxicity.

CSs for HCH are summarized in Table 9-1. Data from which RQs could be derived were not available for δ- or ε-HCH.

9.1.1. α-HCH.

Available long-term studies for α-HCH are summarized in Table 5-6. All studies used oral routes of exposure; five of the six studies were designed to investigate hepatic carcinogenic response (Schulte-Hermann and Parzefall, 1981; Ito et al., 1973a,b, 1975, 1976). The study conducted by Fitzhugh et al. (1950) was conducted for the lifespan of the animal (rats) and examined endpoints other than liver histology, but not all animals started on the test were examined. Despite the latter deficiency, the study by Fitzhugh et al. (1950) is the only study available from which an RQ can be derived.

TABLE 9-1

Oral Composite Scores for HCH^{a}

Isomer	Species	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
α-HCH	rat	40.0^{b}	479	1.5	Early mortality	10	15	1000	Fitzhugh et al., 1950
β-HCH	rat	40.0^{b}	479	1.5	Early mortality	10	15	1000	Fitzhugh et al., 1950
β-HCH	rat	5.0^{b}	60	2.8	Reduced body weight	4	11	1000	Fitzhugh et al., 1950
γ-HCH	rat	17.6	21^{c}	3.5	Testicular atrophy	7	25	100	Dikshith et al., 1978
γ-HCH	rat	114	1365	1	Increased resorptions	8	8	1000	Dzierzawski, 1977
γ-HCH	rat	1.55	1.86^{c}	5.1	Degenerative changes in kidney	6	31	100	Research and Consulting Co., Ltd., 1983
γ-HCH	dog	22.5	27^{c}	3.4	Hematological effects (decreased erythrocytes and reticulocytes; crenated red cells; myeloid to erythroid ratio of 750:1)	4	24	100	Earl et al., 1970
T-HCH	rat	19.8^{d}	24^{c}	3.4	Histological and histochemical changes in adrenals indicative of steroidogenic inhibition	7	24	100	Shivanandappa et al., 1982
T-HCH	rat	40^{b}	479	1.5	Early mortality	10	15	1000	Fitzhugh et al., 1950
T-HCH	mouse	65^{e}	343	1.7	Testicular atrophy	7	12	1000	Nigam et al., 1979
T-HCH	mouse	10	53	2.9	Corneal opacity; slight tendency to convulse	7	20	1000	Kashyap et al., 1979

[a] In all cases, the body weight of a rat, mouse and dog was assumed to be 0.35, 0.03 and 12.7 kg, respectively.

[b] A food factor of 0.05 was assumed in the calculation of this value from ppm diet.

[c] The animal dose was divided by an uncertainty factor of 10 ($\leq$90-day study) prior to adjustment.

[d] 625 mg/rat/90 days (reported) ÷ (0.35 kg/rat x 90 days) = 19.8 mg/kg/day

[e] A food factor of 0.13 was assumed in the calculation of this value from ppm diet.

A CS of 15 can be derived from the lifetime rat study by Fitzhugh et al. (1950) (Table 9-2). A FEL of 800 ppm can be defined on the basis of a significantly reduced lifespan. Assuming that a rat consumes the equivalent in food of 5% of its body weight/day, 800 ppm is equivalent to an animal dose of 40 mg/kg/day. Multiplying 40 mg/kg/day by the product of the cube root of the ratio of rat to human body weight and human body weight (70 kg) yields a human MED of 479 mg/day, which warrants an RV_d of 1.5. An RV_e of 10 can be assigned on the basis of early mortality. Multiplying the RV_e by the RV_d yields a CS of 15, which corresponds to an RQ for α-HCH of 1000 (see Table 9-2).

9.1.2. β-HCH. The available long-term studies on β-HCH are summarized in Table 5-7. Most of these studies were designed to investigate hepatic carcinogenic response (Ito et al., 1973a,b, 1975). Thorpe and Walker (1973) investigated multiple endpoints but observed no effects aside from those related to development of liver tumors. Fitzhugh et al. (1950) conducted a lifetime dietary study on rats and investigated multiple endpoints, but did not examine all animals (rats) that were started on the test. Despite the latter deficiency, Fitzhugh et al. (1950) is the only study that provides appropriate data from which an RQ can be derived (Table 9-3).

The lifetime oral rat study by Fitzhugh et al. (1950) provides a FEL of 800 ppm for significantly reduced lifespan and a LOAEL of 100 ppm for significantly reduced body weight. The highest CS is obtained from the FEL in the following manner. Assuming that a rat consumes the equivalent in food of 5% of its body weight/day, 800 ppm is equivalent to an animal dose of 40 mg/kg/day. Assuming that a rat weighs 0.35 kg, a human MED of 479 mg/day is obtained by multiplying the animal dose by the product of the cube root of the ratio of rat weight to human body weight and by human body

TABLE 9-2

α-HCH

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	479 mg/day
Effect:	early mortality
Reference:	Fitzhugh et al., 1950
RV_d:	1.5
RV_e:	10
Composite Score:	15
RQ:	1000

---

*Equivalent human dose

TABLE 9-3

B-HCH

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route: oral

Dose*: 479 mg/day

Effect: early mortality

Reference: Fitzhugh et al., 1950

RV_d: 1.5

RV_e: 10

Composite Score: 15

RQ: 1000

---

*Equivalent human dose

weight (70 kg); this MED warrants an RV_d of 1.5. An RV_e of 10 can be assigned on the basis of early mortality. Multiplying the RV_d by the RV_e yields a CS of 15, which corresponds to an RQ for β-HCH of 1000 (see Table 9-3).

9.1.3. γ-HCH (Lindane). Long-term oral studies on γ-HCH have associated exposure to HCH with nonneoplastic liver changes (Dikshith et al., 1978; Fitzhugh et al., 1950; Research and Consulting Co., Ltd., 1983; Oesch et al. 1982; Ito et al., 1973a; Rivett et al., 1978), kidney changes (Fitzhugh et al., 1950; Research and Consulting Co., Ltd., 1983), hematological effects (Earl et al., 1970; Morgan et al., 1980) and neurotoxicity (Fitzhugh et al., 1950; Czegledi-Janko and Avar, 1970) (see Table 5-8). Short-term studies suggest that γ-HCH may cause immunosupression (Dewan et al., 1980; Desi et al., 1978) (see Section 5.5.).

Orally-administered γ-HCH was not found to be teratogenic or fetotoxic in Wistar rats (Khera et al., 1979). CD rats (Palmer et al., 1978a), CFY rats (Palmer et al., 1978b), New Zealand White rabbits (Palmer et al., 1978b) or CD-1 mice (Chernoff and Kavlock, 1983; Gray and Kavlock, 1984). In contrast, a study by Dzierzawski (1977) reported increased numbers of resorbed fetuses in hamsters (40 mg/kg on day 9 of gestation), rabbits (40 or 60 mg/kg on day 9 of gestation) and rats (40, 50 or 100 mg/kg on various days of gestation). Maternal toxicity was not reported. These doses are higher than any of those tested in the negative studies, though Chernoff and Kavlock (1983) reported that 25 mg/kg/day was the maximum dose that was not toxic to maternal CD-1 mice.

Palmer et al. (1978a) observed no adverse effects on reproduction in three generations of CD rats fed up to 100 ppm γ-HCH in the diet.

Dikshith and Datta (1977) and Dikshith et al. (1978), however, observed testicular atrophy in ITRC rats gavaged with 17.6 mg γ-HCH/kg in peanut oil for 90 days, suggesting that γ-HCH may have adverse effects on reproduction.

Studies that provide adequate information for the derivation of an RQ for γ-HCH are those of Dikshith et al. (1978), Fitzhugh et al. (1950), Research and Consulting Co., Ltd. (1983), Earl et al. (1970) and Dzierzawski (1977).

Dikshith et al. (1978) observed a LOAEL of 17.6 mg/kg/day for testicular atrophy in ITRC rats fed γ-HCH for 90 days. Fitzhugh et al. (1950) observed early mortality, gross and histologically-defined kidney damage and nervous symptoms and convulsions in rats fed 800 ppm γ-HCH for life. The Research and Consulting Co., Ltd. (1983) reported degenerative histological changes in the kidneys of rats fed γ-HCH (1.55 mg/kg/day) for 12 weeks. Earl et al. (1970) reported hematological effects in dogs fed γ-HCH (22.5 mg/kg/day) for 24 weeks. Dzierzawski (1977) observed increased numbers of resorptions in rats, rabbits and hamsters given 40 mg γ-HCH/kg/day on ≥ 1 days of gestation.

Although each of these studies has some deficiencies (short duration, incomplete examination of animals, small numbers of animals), taken collectively, the studies indicate that the RQ for γ-HCH is 1000. The study that provided the highest CS (17) is the Research and Consulting Co., Ltd. (1983) study. The LOAEL of 1.55 mg/kg/day for kidney damage is assigned an RV_e of 6. Dividing 1.55 mg/kg/day by an uncertainty factor of 10 (for less-than-chronic exposure) then multiplying by the product of the cube root of the ratio of rat body weight to human body weight (assuming a body weight of 0.35 kg for rats) and by the human body weight (70 kg), yields a human

MED of 1.86 mg/day; this is equivalent to an RV_d of 5.1. Multiplying the RV_d by the RV_e yields a CS of 31, which corresponds to an RQ of 100 (Table 9-4).

9.1.4. T-HCH. Long-term oral administration of T-HCH has been shown to adversely affect the liver (Fitzhugh et al., 1950; Barros and Saliba (1978), Barros et al., 1982; Shivanandappa and Krishnakamuri, 1981; Nigam et al., 1982, 1984a,b; Munir and Bhide, 1984), kidney (Fitzhugh et al., 1950; Barros and Saliba, 1978; Barros et al., 1982; Shivanandappa and Krishnakamuri, 1981), adrenal cortex (Shivanandappa and Krishnakamuri, 1981; Shivanandappa et al., 1982) and CNS (Shivanandappa and Krishnakamuri, 1981; Kashyap et al., 1979). Kashyap et al. (1979) also reported that long-term oral exposure to T-HCH was associated with increased corneal opacity.

The teratogenic effects of T-HCH have not been investigated. Nigam et al. (1979) and Shivanandappa and Krishnakamuri (1981, 1983) have shown that orally-administered T-HCH causes testicular atrophy in rats and mice ($\geq$800 ppm, rats; 500 ppm, mice) (see Table 5-10).

Studies that demonstrated adverse effects at the lowest levels of exposure are those of Fitzhugh et al. (1950), Shivanandappa et al. (1982), Nigam et al. (1979) and Kashyap et al. (1979). Fitzhugh et al. (1950) observed early mortality and degenerative changes in the kidneys and testes of rats fed 800 ppm γ-HCH for life. Shivanandappa et al. (1982) reported gross, histological and histochemical changes in the adrenal glands of rats fed 750 ppm γ-HCH (625 mg/rat/90 days) for 90 days. Testicular atrophy was observed among mice fed 500 ppm γ-HCH for 10 months (Nigam et al., 1979), and corneal opacity and a slight tendency to convulse were observed among mice fed 100 ppm γ-HCH or gavaged with 10 mg γ-HCH/kg/day for 80 weeks (Kashyap et al., 1979).

TABLE 9-4

γ-HCH

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	1.86 mg/day
Effect:	degenerative changes in kidney
Reference:	Research and Consulting Co., Ltd., 1983
RV_d:	5.1
RV_e:	6
Composite Score:	31
RQ:	100

---

*Equivalent human dose

The study of Shivanandappa et al. (1982) yields the highest composite score. The animal dose of 19.8 is adjusted to a human MED of 24 mg/day in the following manner. The animal dose is first divided by an uncertainty factor of 10 to account for less than chronic exposure. This yields an adjusted animal dose of 1.98 mg/kg/day. An MED of 24 is obtained by multiplying 1.98 by the product of the cube root of the ratio of rat body weight (0.35 kg, assumed) to human body weight (70 kg). An RV_d of 3.4 is assigned on the basis of the MED. An RV_e of 7 is assigned on the basis of histological and histochemical adrenal changes indicative of steroidogenic inhibition. Multiplying the RV_d by the RV_e yields a composite score of 24. The RQ for T-HCH is therefore 100 (Table 9-5).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

9.2.1. α-HCH. Dietary α-HCH has been shown to cause an increased incidence of liver tumors in five strains of mice (Ito et al., 1973a,b, 1976; Nagasaki et al., 1972a, 1975; Hanada et al., 1973; Goto et al., 1972) and in Wistar rats (Ito et al., 1975; Schulte-Hermann and Parzefall, 1981). The teratogenic and reproductive effects of α-HCH have not been investigated. Nonneoplastic hepatic changes have occurred in rats and mice fed α-HCH (Shulte-Hermann and Parzefall, 1981; Ito et al., 1973a,b, 1975, 1976; Fitzhugh et al., 1950).

According to IARC (1979), as well as the EPA Guidelines for Cancer Assessment (U.S. EPA, 1986b), there is sufficient evidence to conclude that α-HCH is carcinogenic to mice. Since there are no human data available, α-HCH is placed in IARC Group 2B and EPA Group B2, meaning that α-HCH is considered probably carcinogenic to man. Data for the positive studies that reported incidences of histologically verified tumors are summarized in Tables 9-6 through 9-12. Positive studies lacking this type of incidence

TABLE 9-5

T-HCH

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	24 mg/day
Effect:	histological and histochemical adrenal changes indicative of steroidogenic inhibition
Reference:	Shivanandappa et al., 1982
RV_d:	3.4
RV_e:	7
Composite Score:	24
RQ:	100

---

*Equivalent human dose

TABLE 9-6

Incidence of Liver Neoplasms in Male DDY Mice Fed α-HCH (>99% pure) in the Diet[a]

Dose (ppm)	Duration of Exposure (weeks)	Duration of Study (weeks)	Tumor Incidence[b]
0	NA	72	0/18
500	16	16	5/21
500	20	20	14/20
500	20	24	8/20
500	20	28	5/20
500	20	32	2/19
500	24	24	20/20
500	24	28	18/19
500	24	32	9/16
500	24	36	7/17
500	24	40	8/16
500	24	48	12/15
500	24	60	14/14
500	36	36	14/14
500	36	48	11/13
500	36	60	12/12
500	36	72	13/13

QUALITY OF EVIDENCE

Strengths of study:	time-to-tumor information; comprehensive examination of the liver
Weakness of study:	short duration of exposure
Overall adequacy:	adequate
Comments:	100% response was observed at $\geq$24 weeks of exposure. Hepatocellular carcinoma was the predominant tumor type 60-70 weeks from the beginning of the study.

---

[a] Source: Ito et al., 1976

[b] Combined incidence of hepatocellular carcinoma and nodular hyperplasia

NA = Not applicable

TABLE 9-7

Incidence of Hepatic Neoplasms in Mice Fed α-HCH for 24 Weeks[a,b]

Strain	Sex	Dose (ppm)	Incidence of Tumors[c]	
			Nodular Hyperplasia	Hepatocellular Carcinoma
DDY	M	0	0/16	0/16
	M	500	20/20	6/20
	M	0	0/20	0/20
	M	500	20/20	13/20
	F	0	0/20	0/20
	F	500	16/20	5/20
ICR	M	0	0/20	0/20
	M	500	18/23	8/23
	F	0	0/19	0/19
	F	500	15/29	6/29
DBA/2	M	0	0/13	0/13
	M	500	8/16	1/16
	F	0	0/16	0/16
	F	500	5/15	1/15
C57BL/6	M	0	0/22	0/22
	M	500	4/21	0/21
	F	0	0/16	0/16
	F	500	3/18	0/18
C3H/He	M	0	0/17	0/17
	M	500	13/20	0/20
	F	0	0/18	0/18
	F	500	11/20	2/20

TABLE 9-7 (cont.)

QUALITY OF EVIDENCE

Strengths of study:	five strains and both sexes tested
Weaknesses of study:	purity of compound not reported; short duration of exposure
Overall adequacy:	adequate

---

[a] Source: Nagasaki et al., 1975

[b] Purity not reported

[c] Combined incidence not reported

TABLE 9-8

Incidence of Liver Neoplasms in Male dd Mice fed α-HCH (>99% pure) in the Diet for 24 Weeks[a]

Dose (ppm)	Duration of Study (weeks)	Incidence of Tumors[b]	
		Nodular Hyperplasia	Hepatocellular Carcinoma
0	24	0/20	0/20
50	24	0/28	0/28
100	24	0/26	0/26
250	24	23/30	8/30

QUALITY OF EVIDENCE

Strengths of study:	three different doses tested; relatively large number of mice examined/treatment
Weaknesses of study:	short duration of exposure; only the liver was examined microscopically
Overall adequacy:	limited

---

[a] Source: Ito et al., 1973b

[b] Combined incidence not reported

TABLE 9-9

Incidence of Liver Neoplasms in Male dd Mice fed α-HCH (>99% pure) in the Diet for 24 Weeks[a]

Dose (ppm)	Duration of Study (weeks)	Incidence of Tumors		
		Nodular Hyperplasia	Hepatocellular Carcinoma	Combined[b]
0	24	0/20	0/20	0/20
100	24	0/20	0/20	0/20
250	24	30/38	10/38	30/38
500	24	20/20	17/20	20/20

QUALITY OF EVIDENCE

Strengths of study:	three doses tested; relatively large number of mice/treatment
Weaknesses of study:	short duration of exposure; only the liver was examined microscopically
Overall adequacy:	adequate

---

[a] Source: Ito et al., 1973a

[b] Combined incidence of nodular hyperplasia and hepatocellular carcinoma

TABLE 9-10

Incidences of Hepatomas in dd Mice Fed α-HCH in the Diet for 32 Weeks[a,b]

Sex	Dose (ppm)	Duration of Study (weeks)	Tumor Incidence[c]
M	0	37-38	0/14
	100	37-38	1/8
	300	37-38	7/7
	600	37-38	7/7
F	0	37-38	0/15
	100	37-38	0/8
	300	37-38	2/3
	600	37-38	6/8

QUALITY OF EVIDENCE

Strengths of study:	three levels of exposure
Weaknesses of study:	small numbers of mice/treatment; only livers were examined histologically; the purity of α-HCH was not reported
Overall adequacy:	limited

---

[a] Source: Hanada et al., 1973

[b] Purity not reported

[c] Number of mice started on test was 10-11/sex for each treated group and 20-21/sex for controls. Only mice that survived $\geq$36 weeks were examined.

TABLE 9-11

Incidences of Liver Neoplasms in Male Wistar Rats Fed α-HCH (>99% pure) in the Diet[a]

Dose (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Tumor Incidence[b] Nodular Hyperplasia	 Hepatocellular Carcinoma
0	NA	72	0/8	0/8
500	24	24	0/6	0/6
500	48	48	0/5	0/5
1000	24	24	0/8	0/8
1000	48	48	5/12	0/12
1000	72	72	12/16	1/16
1500	72	72	10/13	3/13

QUALITY OF EVIDENCE

Strengths of study:	three doses used; time-to-tumor information; all major organs examined
Weakness of study:	small numbers of rats/treatment
Overall adequacy:	limited

---

[a] Source: Ito et al., 1975

[b] Combined incidence not reported; rats that died during the experiment were not examined.

NA = Not applicable

TABLE 9-12

Incidences of Liver Neoplasms in Female Wistar Rats Exposed Orally to α-HCH (99.5%) pure)[a]

Vehicle	Dose and Duration	Age at Death[b] (months)	Tumor Incidence
NA	0 mg/kg/day	9-10	0/4
Diet	~20 mg/kg/day for 8 months	9-10	0/3
Vegetable oil	420 mg/kg every 3rd week for 7 months	9-10	0/1
NA	0 mg/kg/day	12	0/9
Vegetable oil	200 mg/kg every 2nd week for 12 months	12	3/8
NA	0 mg/kg/day	14-19	0/3
Diet	~20 mg/kg/day for 13.5-17 months	14-19	2/4
Vegetable oil	420 mg/kg every 3rd week for 11.6-16 months	14-19	1/4
NA	0 mg/kg/day	23-34.5	1/6
Diet	~20 mg/kg/day for 20-26 months	23-34.5	6/6[c]
Vegetable oil	420 mg/kg every 3rd week for 21.5-33 months	23-34.5	7/8[d]

QUALITY OF EVIDENCE

Strengths of study:	sufficient duration of exposure; time-to-tumor information
Weaknesses of study:	small numbers of rats/group; liver was the only organ examined
Overall adequacy:	limited

---

[a] Source: Schulte-Hermann and Parzefall, 1981

[b] Rats were ~1.25-2 months old at start of treatment

[c] Combined incidences of neoplastic nodules and hepatocellular carcinomas

[d] One of these tumors was a hepatocellular carcinoma

NA = Not applicable

data (Nagasaki et al., 1972a; Goto et al., 1972) and a negative study (Fitzhugh et al., 1950) are summarized in Table 5-1.

The study that provides the best estimate of carcinogenic potency is that of Ito et al. (1973a); an adjusted potency factor of 69.5 (mg/kg/day)$^{-1}$ is based on an increased incidence of liver neoplasms in male dd mice fed 100, 250 and 500 ppm α-HCH for 24 weeks (Table 9-13). The potency factor was adjusted for body weight and less-than-lifetime exposure [unadjusted $1/ED_{10} \times (70/0.03)^{1/3}) \times (104/24)^{a}$]. The currently recommended $1/ED_{10}$ of 69.5 (mg/kg/day)$^{-1}$ is thus different from the value of 211 reported by U.S. EPA (1984b); the U.S. EPA (1984b) value apparently was based on the data of Ito et al. (1976). A potency factor of 69.5 (mg/kg/day)$^{-1}$ (Potency Group 3) and an EPA Group rating of B2 place α-HCH in the MEDIUM category of the CERCLA hazard ranking scheme.

9.2.2. β-HCH. Dietary β-HCH has been shown to cause an increased incidence of liver tumors in CF1 mice (Thorpe and Walker, 1973) but not in dd mice (Ito et al., 1973a,b; Hanada et al., 1973; Nagasaki et al., 1972b) or Wistar rats (Ito et al., 1975; Fitzhugh et al., 1950). As previously discussed (see Section 5.1.1.), an additional report (Goto et al., 1972) indicates that mice fed 600 ppm of β-HCH had no grossly observable liver nodules but had histological evidence of benign hepatomas (incidence not specified).

According to IARC criteria, and the EPA cancer guidelines (U.S. EPA, 1986b), there is limited evidence that β-HCH is carcinogenic to mice. Since there were no human data available, β-HCH is placed in EPA Group C, meaning β-HCH is considered a possible human carcinogen. Incidence data for the only study that provided positive results and actual incidences (Thorpe and Walker, 1973) are summarized in Table 9-14. Negative studies are summarized in Table 5-2.

TABLE 9-13

Derivation of Potency Factor (F) for α-HCH

Reference:	Ito et al., 1973a			
Exposure route:	oral			
Species:	mouse			
Strain:	dd			
Sex:	male			
Vehicle or physical state:	diet			
Body weight:	0.03 kg (assumed)			
Duration of treatment:	24 weeks			
Duration of study:	24 weeks			
Lifespan of animal:	104 weeks			
Target organ:	liver			
Tumor type:	nodular hyperplasia and hepatocellular carcinoma			
Experimental doses/exposure (ppm):	0	100	250	500
Transformed doses (mg/kg/day)[a]:	0	13.0	37.5	65
Tumor incidence[b]:	0/20	0/20	10/38	20/20
Unadjusted 1/ED$_{10}$:	0.0644114			
1/ED$_{10}$ (F Factor):	69.5 (mg/kg/day)$^{-1}$			

---

[a] Assumes a food factor of 0.13

[b] GLOBAL 82 and GLOBAL 79 will not converge when there are only two levels of treatment and 100% response in one of the groups. It was therefore necessary to reduce the incidence to a value <100% and to adjust the dose proportionally.

TABLE 9-14

Incidence of Liver Neoplasms in CF1 Mice Fed B-HCH (>99% pure) in the Diet for up to 110 Weeks[a]

Sex	Duration of Exposure	Dose (ppm)	Tumor Incidence[b] (p value, 2x2 Exact Test)
M	0-17 months[c]	0	0/4
		200	6/13 (<0.05)
	0-21 months[c]	0	2/18
		200	10/17 (<0.05)
	0-25 months[c]	0	2/25
		200	18/26 (<0.01)
	26 months[d]	0	9/20
		200	4/4 (>0.05)
	Total (0-26 months)	0	11/45
		200	22/29 (<0.01)
	Adjusted total incidence[e]	0	11/45
		200	22/24 (<0.01)
F	0-17 months[c]	0	0/4
		200	2/16 (<0.01)
	0-21 months[c]	0	0/11
		200	5/20 (<0.01)
	0-25 months[c]	0	5/30
		200	9/25 (>0.05)
	26 months[d]	0	5/14
		200	4/5 (>0.05)
F	Total (0-26 months)	0	10/44
		200	13/30 (>0.05)
	Adjusted total incidence[e]	0	10/44
		200	13/19 (<0.01)

TABLE 9-14 (cont.)

QUALITY OF EVIDENCE

Strengths of study:	study was conducted over the lifespan of the animal; comprehensive histological examination was performed; time-to-tumor information
Overall adequacy:	adequate

---

[a] Source: Thorpe and Walker, 1973

[b] Combined incidence of hyperplastic nodules and hepatocellular carcinoma

[c] These are cumulative incidences for mice that died and were subsequently examined.

[d] The incidences are for mice killed at the end of the experiment.

[e] Incidence subsequent to the finding of the first tumor in any tissue in each group of mice (i.e., excluding mice examined before the first tumor)

An adjusted potency factor of 10.7 can be derived on the basis of an increased combined incidence of hepatic hyperplastic nodules and hepatocellular carcinomas in male CF1 mice fed 200 ppm β-HCH in the diet for 110 weeks (Thorpe and Walker, 1973). This value was obtained by multiplying the unadjusted potency factor by the cube root of the ratio of human body weight (70 kg) to mouse body weight (0.03 kg). Adjustment for less-than-lifetime exposure was not necessary since the mice were treated for 110 weeks (Table 9-15). The potency factor of 1.7 reported in U.S. EPA (1984b) was derived from the Thorpe and Walker (1973) study, but was based on malignant liver tumors only. The value of 10.7 is based on the combined incidence of benign and malignant hepatic tumors and is therefore the recommended value.

A chemical with a potency factor of 10.7 and a EPA Group C Classification has a LOW hazard ranking under CERCLA.

9.2.3. γ-HCH (Lindane). Dietary γ-HCH was shown to cause a definite increase in the incidence of liver tumors in male CF1 mice fed 400 ppm for 110 weeks (Thorpe and Walker, 1973). Borderline responses were also observed in two other studies in male dd mice fed 600 ppm for 32 weeks and examined 5-6 weeks after treatment (Hanada et al., 1973), and in male ICR-JCL mice fed 600 ppm for 26 weeks (Goto et al., 1972). No liver tumors were observed in dd mice fed up to 500 ppm for 24 weeks (Ito et al., 1973a,b; Nagasaki et al., 1972a) or in Wistar rats fed 500 ppm for up to 48 weeks (Ito et al., 1975). Significant compound-related development of tumors of any type was not observed in NMRI mice (Herbst et al., 1975; Weisse and Herbst, 1977), B6C3F1 mice (NCI, 1977), Osborne-Mendel rats (NCI, 1977) or Wistar rats (Fitzhugh et al., 1950). The study conducted by NCI (1977) has been criticized for poor survival (rats), changes in dosing regime and the possibility that male rats did not receive MTDs (IARC, 1979). The negative findings of Fitzhugh et al. (1950) are also

TABLE 9-15

Derivation of Potency Factor (F) for β-HCH

Reference:	Thorpe and Walker, 1973	
Exposure route:	oral	
Species:	mouse	
Strain:	CF1	
Sex:	male	
Vehicle or physical state:	diet	
Body weight:	0.03 kg	
Duration of treatment:	110 weeks	
Duration of study:	110 weeks	
Lifespan of animal:	110 weeks	
Target organ:	liver	
Tumor type:	hyperplastic nodules and hepatocellular carcinoma	
Experimental doses/exposure (ppm):	0	200
Transformed doses (mg/kg/day)*:	0	26
Tumor incidence:	11/45	22/24
Unadjusted $1/ED_{10}$:	0.804783634	
$1/ED_{10}$ (F Factor):	10.7	

*Assumes a food factor of 0.13

inconclusive since only small numbers of animals were examined histologically. The negative findings of Ito et al. (1973a,b), Nagasaki et al. (1972a) and Ito et al. (1975) might be attributed to small numbers of animals and short duration of study.

Incidence data for the positive studies that reported incidences of histologically verified tumors are summarized in Tables 9-16 and 9-17. A positive study lacking this type of incidence data (Goto et al., 1972) and negative studies are summarized in Table 5-3. According to IARC criteria, and EPA guidelines (U.S. EPA, 1986b), there is sufficient evidence in one study and in two borderline studies that give rise to some uncertainty about the strength of carcinogenic evidence in animals. Notably a metabolite of lindane, 2,4,6-trichlorophenol has a Group B2 weight of evidence and this metabolite has been identified in both exposed rodents and humans. Since there are no human data available, γ-HCH is placed EPA Group B2-C (i.e., between Groups B2 and C) (U.S. EPA, 1985a, 1986a). This range reflects some uncertainty in the strength of the animal carcinogenicity data.

The study that provides the best estimate of carcinogenic potency is that of Thorpe and Walker (1973). An adjusted potency factor of 7.4 can be estimated from this study and is based on the increased combined incidence of hyperplastic nodules and hepatocellular carcinomas in male CF1 mice fed 400 ppm γ-HCH for 110 weeks (Table 9-18). The adjusted value was obtained by multiplying the animal value (unadjusted value) by the cube root of the ratio of human body weight (70 kg) to mouse body weight (0.03 kg). Adjustment for less-than-lifetime exposure was not necessary since mice were exposed for 110 weeks. This potency factor of 7.4 differs from the value of 1.7 reported by U.S. EPA (1984b); the U.S. EPA (1984b) value was also based on the data of Thorpe and Walker (1983) but was estimated on the basis of

TABLE 9-16

Incidence of Hepatomas in dd Mice Fed γ-HCH in the Diet for 32 Weeks and Examined After 37-38 Weeks[a]

Sex	Dose (ppm)	Tumor Incidence[b]
M	0	0/14
	100	0/10
	300	0/9
	600	3/4
F	0	0/15
	100	0/8
	300	0/7
	600	1/3

QUALITY OF EVIDENCE

Strengths of study:	three doses tested; organs other than liver examined
Weaknesses of study:	short duration; small numbers of mice/treatment; purity of compound was not specified; survival in 600 ppm group was poor
Overall adequacy:	limited

---

[a] Source: Hanada et al., 1973

[b] Number of mice started on test was 10-11/sex for each treated group and 20-21/sex for controls. Only mice that survived ≥ 36 weeks were examined.

TABLE 9-17

Incidence of Liver Neoplasms in CF1 Mice Fed γ-HCH (>99.5% pure) in the Diet for up to 110 Weeks[a]

Sex	Duration of Exposure	Dose (ppm)	Tumor Incidence[b] (p value, 2x2 Exact Test)
M	0-17 months[c]	0	0/6
		400	6/86 (<0.01)
	0-21 months[c]	0	2/11
		400	14/15 (<0.01)
	0-25 months[c]	0	2/25
		400	23/24 (<0.01)
	26 months[d]	0	9/20
		400	4/5
	Total (0-26 months)	0	11/45
		400	27/29 (<0.01)
	Adjusted total incidence[e]	0	11/45
		400	27/28 (<0.01)
F	0-17 months[c]	0	0/4
		400	9/18 (<0.01)
	0-21 months[c]	0	0/11
		400	14/23 (<0.01)
	0-25 months[c]	0	5/30
		400	19/28 (<0.01)
	26 months[d]	0	5/14
		400	1/1 (<0.05)
F	Total (0-26 months)[e]	0	10/44
		400	20/29 (<0.05)
	Adjusted total incidence[e]	0	10/44
		400	20/21 (<0.05)

TABLE 9-17 (cont.)

QUALITY OF EVIDENCE

Strengths of study: study was conducted over the lifespan of the animal; comprehensive histological examination was performed; time-to-tumor information given

Overall adequacy: adequate

---

[a] Source: Thorpe and Walker, 1973

[b] Combined incidence of hyperplastic nodules and hepatocellular carcinomas

[c] These are cumulative incidences for mice that died and were subsequently examined.

[d] The incidences are for mice killed at the end of the experiment.

[e] Incidence subsequent to the finding of the first tumor in any tissue in each group of mice.

TABLE 9-18

Derivation of the Potency Factor (F) for γ-HCH

Reference:	Thorpe and Walker, 1973	
Exposure route:	oral	
Species:	mouse	
Strain:	CF1	
Sex:	male	
Vehicle or physical state:	diet	
Body weight:	0.03 kg	
Duration of treatment:	110 weeks	
Duration of study:	110 weeks	
Lifespan of animal:	110 weeks	
Target organ:	liver	
Tumor type:	hyperplastic nodules and hepatocellular carcinoma	
Experimental doses/exposure (ppm):	0	400
Transformed doses (mg/kg/day)*:	0	52
Tumor incidence:	11/45	27/28
Unadjusted $1/ED_{10}$:	0.557044101	
$1/ED_{10}$ (F Factor):	7.4	

*Assumes a food factor of 0.13

malignant liver tumors only. The potency factor of 7.4 is based on the combined incidence of benign and malignant liver tumors and is therefore the recommended value.

A potency factor of 7.4 and a CAG Group rating of B2-C place γ-HCH in the MEDIUM-LOW categories of the CERCLA hazard ranking scheme.

9.2.4. δ-HCH. Dietary δ-HCH did not cause neoplastic or nonneoplastic changes in the livers of male dd mice (Ito et al., 1973a; Nagasaki et al., 1972a) or male Wistar rats (Ito et al., 1975). These studies used small numbers of animals and were conducted for only 24 weeks. Goto et al. (1972) reported that a mixture of δ- and ε-HCH caused an increased incidence of benign and malignant hepatomas in male ICR-JCL mice after 26 weeks of dietary administration, but the individual isomers were not tested. There were no human data available.

According to the EPA cancer guidelines (U.S. EPA, 1980), there is limited evidence that δ-HCH is carcinogenic in animals. Therefore, δ-HCH is placed in EPA Group C, but it is not possible to derive a potency factor. Accordingly, a default potency category of 2 is assigned. A potency Group of 2 and a Group C weight-of-evidence result in a LOW hazard ranking under CERCLA.

9.2.5. ε-HCH. Data pertaining to the carcinogenic effects of ε-HCH could not be located in the available literature as cited in the Appendix. Goto et al. (1972) reported that a mixture of δ-HCH and ε-HCH caused an increased incidence of benign and malignant hepatomas in male ICR-JCL mice after 26 weeks of dietary administration, but the individual isomers were not tested.

According to the EPA cancer guidelines (U.S. EPA, 1980), there is limited evidence that ε-HCH is carcinogenic in animals. Therefore, ε-HCH falls into EPA Group C, and it is not possible to derive a potency factor. Accordingly, a default potency category of 2 is assigned. A potency Group of 2 and a Group C weight-of-evidence result in a LOW hazard ranking under CERCLA.

9.2.6. T-HCH. T-HCH has been shown to cause increased incidences of liver neoplasms in four strains of mice (Hanada et al., 1973; Goto et al., 1972; Kashyap et al., 1979; Nigam et al., 1984a; Bhatt et al., 1981; Munir et al., 1983; Nagasaki et al., 1971, 1972b; Munir and Bhide, 1984) but not in Wistar rats (Munir et al., 1983) or Syrian golden hamsters (Munir et al., 1983).

According to the EPA cancer guidelines (U.S. EPA, 1986b), there is sufficient evidence to conclude that T-HCH is carcinogenic to animals. Since there are no human data available, T-HCH is placed in EPA Group B2. This is interpreted to indicate that T-HCH is probably carcinogenic to humans. Incidence data from the positive studies that reported incidences of histologically verified tumors are summarized in Tables 9-19 through 9-23. Positive studies lacking this type of data and negative studies are summarized in Table 5-5.

The study that provides the best estimate of carcinogenic potency is that of Munir et al. (1983). An adjusted potency factor of 8.08 is based on an increased incidence of benign and malignant liver tumors in male Swiss mice fed 0, 125 or 250 ppm T-HCH from 8-10 weeks of age to 15-17 months of age (Table 9-24). The potency factor was adjusted for body weight and less-than-lifetime exposure [unadjusted $1/ED_{10}$ x $(70/0.03)^{1/3}$ x $(24/15)^3$] (Table 9-25).

TABLE 9-19

Incidence of Hepatomas in dd Mice Fed T-HCH in the Diet for 32 Weeks and Examined 5-6 Weeks Posttreatment[a]

Sex	Dose (ppm)	Tumor Incidence[b]
M	0	0/14
	100	0/10
	300	4/4
	600	4/4
F	0	0/15
	100	0/8
	300	3/5
	600	5/5

QUALITY OF EVIDENCE

Strengths of study:	three doses tested
Weaknesses of study:	small numbers of mice/treatment; short duration of exposure; isomeric composition not specified
Overall adequacy:	limited

---

[a] Source: Hanada et al., 1973

[b] Number of mice started on test was 10-11/sex for each treated group and 20-21/sex for controls. Only mice that survived ≥36 weeks were examined.

TABLE 9-20

Incidence of Liver Neoplasms in Male dd Mice Fed T-HCH in the Diet for 24 Weeks[a,b]

Dose (ppm)	Tumor Incidence[c]
0	0/14
6.6	0/20
66	0/20
660	20/20

QUALITY OF EVIDENCE

Strengths of study:	composition of compound reported; three doses tested; histopathological examinations were performed on major organs
Weaknesses of study:	short duration of exposure
Overall adequacy:	adequate

---

[a] Source: Nagasaki et al., 1971, 1972b; Nagasaki, 1973

[b] 66.5% α-HCH, 11.4% β-HCH, 15.2% γ-HCH, 6.4% δ-HCH and 0.5% "other"

[c] Combined incidence of hyperplastic nodules and hepatomas

TABLE 9-21

Incidence of Tumors in Swiss Mice Exposed Orally to T-HCH for 80 Weeks[a,b]

Sex	Route/Vehicle	Dose	Mice with Tumors	Mice with Liver Tumors	Mice with Reticulum Cell Tumors Leukemias or Lymphomas
M	NA	0	9/25	4/25	2/25
	oral/diet	100 ppm	22/23	16/23	3/23
	gavage/olive oil	10 mg/kg/day	17/26	12/26	2/26
F	NA	0	5/26	1/26	3/26
	oral/diet	100 ppm	21/25	9/25	12/25
	gavage/olive oil	10 mg/kg/day	16/28	7/28	6/28

QUALITY OF EVIDENCE

Strengths of study:	80-week study; two types of oral exposure; isomeric composition specified; histological examination of major tissues
Weakness of study:	only one dose tested
Overall adequacy:	adequate

---

[a] Source: Kashyap et al., 1979

[b] 68.7% α-HCH, 6.5% β-HCH and 13.5% γ-HCH; other components not quantified

NA = Not applicable

TABLE 9-22

Incidence of Liver Neoplasms in Male Swiss Mice Fed T-HCH in the Diet*

Dose/Exposure	Duration of Study (months)	Tumor Incidence		
		Neoplastic Nodules	Trabecular Cell Carcinoma	Pulmonary Metastasis
0 ppm/NA	18	0/75	0/75	0/75
500 ppm/2 months	2	0/6	0/6	0/6
500 ppm/2 months	6	0/6	0/6	0/6
500 ppm/2 months	12	0/15	0/15	0/15
500 ppm/4 months	4	0/6	0/6	0/6
500 ppm/4 months	8	0/6	0/6	0/6
500 μpm/4 months	14	6/15	0/15	0/15
500 ppm/6 months	6	4/6	0/6	0/6
500 ppm/6 months	10	5/6	0/6	0/6
500 ppm/6 months	16	7/15	8/15	2/15
500 ppm/8 months	8	2/6	4/6	0/6
500 ppm/8 months	12	2/6	4/6	1/6
500 ppm/8 months	18	3/15	12/15	14/15

QUALITY OF EVIDENCE

Strengths of study:	conducted for most of the animals' lifespan; time-to-tumor information
Weakness of study:	isomeric composition not reported
Overall adequacy:	adequate

---

*Source: Nigam et al., 1984a

TABLE 9-23

Incidence of Liver Neoplasms in Male Swiss Mice fed T-HCH in the Diet from 8-10 Weeks of Age up to 22 Months of Age[a]

Age at Examination (months)	Dose (ppm)	Tumor Incidence[b]
8-11	125	0/10
	250	4/17
	500	28/37
	0	0/22
12-14	125	0/10
	250	9/12
	500	10/10
	0	0/16
15-17	125	8/20
	250	12/12
	500	not examined
	0	2/22[c]
18-22	125	9/15
	250	not examined
	500	not examined
	0	2/22[c]

QUALITY OF EVIDENCE

Strengths of study:	sufficient duration of exposure; several doses tested; time-to-tumor information
Weaknesses of study:	composition of compound not reported; no matched controls[c]
Overall adequacy:	Adequate

---

[a] Source: Munir et al., 1983

[b] Combined incidence of benign hepatic nodules and hepatocellular carcinomas. Control incidences are taken from a similar experiment in male Swiss mice conducted in the same laboratory and reported in the same paper.

[c] Incidence in controls killed at 15-20 months of age (see footnote b)

TABLE 9-24

Incidence of Liver Tumors in Mice Fed T-HCH in the Diet from 8-10 Weeks of Exposure up to 20 Months of Exposure[a]

Strain	Sex	Dose and Duration of Exposure	Age at Examination (months)	Tumor Incidence[b]
Swiss	M	none	8-11	0/22
		none	12-14	0/16
		none	15-20	2/22
	M	500 ppm continuous	8-11	28/37
		500 ppm continuous	12-14	10/10
		500 ppm continuous	15-20	12/12
	M	500 ppm 2 months	8-11	0/15
		500 ppm 2 months	12-14	0/10
		500 ppm 2 months	15-20	0/10
	F	none	8-11	0/20
		none	12-14	0/16
		none	15-20	1/20
	F	500 ppm continuous	8-11	3/16
		500 ppm continuous	12-14	6/16
		500 ppm continuous	15-20	14/14
	F	500 ppm 3 months	8-11	0/10
		500 ppm 3 months	12-14	0/8
		500 ppm 3 months	15-20	11/12
BALB/c	M	none	8-11	0/8
		none	12-14	0/8
		none	15-20	1/15
	M	500 ppm continuous	8-11	9/10
		500 ppm continuous	12-14	10/10
		500 ppm continuous	15-20	NR
	F	none	8-11	0/8
		none	12-14	0/9
		none	15-20	2/20
	F	500 ppm continuous	8-11	7/10
		500 ppm continuous	12-14	10/10
		500 ppm continuous	15-20	NR

TABLE 9-24 (cont.)

QUALITY OF EVIDENCE

Strengths of study:	sufficient duration of exposure; time-to-tumor information; two strains and both sexes examined
Weakness of study:	composition of compound not reported
Overall adequacy:	adequate

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[a] Source: Munir et al., 1983

[b] Combined incidence of benign hepatic nodules and hepatocellular carcinomas

NR = Not reported

TABLE 9-25

Derivation of Potency Factor (F) for T-HCH

Reference:	Munir et al., 1983		
Exposure route:	oral		
Species:	mouse		
Strain:	Swiss		
Sex:	male		
Vehicle or physical state:	diet		
Body weight:	0.03 kg		
Duration of treatment:	from 8-10 weeks of age until 15-17 months of age (~15 months)		
Duration of study:	same as above		
Lifespan of animal:	24 months		
Target organ:	liver		
Tumor type:	benign hepatic nodules and hepatocellular carcinomas		
Experimental doses/exposure (ppm):	0	125	250
Transformed doses (mg/kg/day)*:	0	16.25	32.5
Tumor incidence:	2/22	8/20	12/12
Unadjusted 1/ED$_{10}$:	0.148735599		
1/ED$_{10}$ (F Factor):	8.1		

*Assumes a food factor of 0.13

A potency factor of 8.1 and a CAG Group rating of B2 place T-HCH in the MEDIUM category of the CERCLA ranking scheme. A summary of all HCH cancer data is presented in Section 9.3.

9.3. SUMMARY OF ALL HCH CANCER DATA

The summary of the animal carcinogenicity data for α-, β-, γ-, δ- and ε-HCH is presented in Table 9-26. Such summary considerations indicate that at dietary doses in excess of 100-200 ppm, cancer of the liver often results mainly in the mouse and sometimes in the rat. Tumor occurrence can take place as early as 24-36 weeks following commencement of the HCH dosing regimen. The resulting estimates of cancer potency from a number of studies place the q_1^* parameter in the 1.3-6.3 $(mg/kg/day)^{-1}$ range (corrected for body weight differences and less-than-lifetime dosing schedules). The technical mixture, which is a mixture of the isomers, most closely relates to α-HCH in category B2 and q_1^* comparisons. α-HCH is the largest component at 65%; therefore, it suggests a general additive contribution of the components with the largest (α) imposing the cancer characteristics of T-HCH mixture.

TABLE 9-26

Summary of the Carcinogenicity Evaluation for Hexachlorocyclohexanes of Environmental Concern

HCH Isomer	Animals Responding[a]		Animals Not Responding[a]	Cancer Category	Human Cancer Potency[b] Estimate (q_1*)	$1/ED_{10}$ Cancer Potency F-Factor^{v} (corrected)	CERCLA Hazard Ranking
	Species	Strains					
α-HCH	mouse rat	5 mouse 1 rat	1 rat	B2	6.34 mouse (1.4 rat)	69.5	Medium
β-HCH	mouse	1 mouse	4 mouse 1 rat	C	1.84	10.7	Low
γ-HCH (lindane)	mouse	1 mouse (3 mouse borderline)	2 mouse 2 rats	C/B2 range	1.33	7.4	Low-Medium
δ-HCH		No valid studies		C	--	--	Low
ε-HCH		No valid studies		C	--	--	Low
Technical-grade (T-HCH)	mouse	(2 mouse borderline)	1 mouse 1 rat 1 hamster	B2	1.76	8.1	Medium

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[a] These responses are not all derived from experiments of equivalent power of determination, some being short on the time of dosing, amount of dose, etc. As such, these are weight of evidence evaluations.

[b] Units are $(mg/kg/day)^{-1}$ or reciprocal dose units.

10. REFERENCES

Abel, P.D. 1980. Toxicity of γ-hexachlorocyclohexane (lindane) to Gammarus pulex: Mortality in relation to concentration and duration of exposure. Freshwater Biol. 10(3): 251-259.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985-1986. Threshold limit values for chemical substances in the work environment adopted by ACGIH with intended changes for 1985-1986. Cincinnati, OH. p. 1-114.

Ahdaya, S.M., R.J. Monroe and F.E. Guthrie. 1981. Absorption and distribution of intubated insecticides in fasted mice. Pestic. Biochem. Physiol. 16(1): 38-46.

Ahmed, F.E., R.W. Hart and N.J. Lewis. 1977. Pesticide induced DNA damage and its repair in cultured human cells. Mutat. Res. 42: 161-174.

Allsup, T. and D. Walsh. 1982. Gas chromatographic analysis of chlorophenylmercapturic acid lindane metabolites. J. Chromatogr. 236(2): 421-428. (Cited in U.S. EPA, 1985a)

Altmann, H.J., C. Boehme and H. Uehleke. 1983. Studies on the kinetics of B-HCH in rats and minipigs. In: Hexachlorcyclohexan Schadst. Lebensm., Mater. Zwei Kollog., Meeting date 1979-1980. p. 101-106. (Ger.) [CA 99(23):189331s]

Anderson, D. and J.A. Styles. 1978. An evaluation of 6 short-term tests for detecting organic chemical carcinogens. Appendix 2. The bacterial mutation test. Br. J. Cancer. 37: 924-930.

Angerer, J., R. Heinrich and H. Laudehr. 1981. Occupational exposure to hexachlorocyclohexane. Int. Arch. Occup. Environ. Health. 48(4): 319-324.

Angerer, J., R. Maass and R. Heinrich. 1983. Occupational exposure to hexachlorocyclohexane. VI. Metabolism of γ-hexachlorocyclohexane in man. Int. Arch. Occup. Environ. Health. 51(1): 59-67.

Angerer, J., R. Heinrich and H. Laudehr. 1985. Occupational exposure to hexachlorocyclohexane. Int. Arch. Occup. Environ. Health. 48(4): 319-324. (Cited in U.S. EPA, 1985a)

Arthur, R.D., J.D. Cain and B.F. Barrentine. 1976. Atmospheric levels of pesticides in the Mississippi delta. Bull. Environ. Contam. Toxicol. 15: 129-134.

Babu, K.A., S.K. Nigam, B.C. Lakkad, et al. 1981. Effect of hexachlorocyclohexane on somatic and meiotic divisions in male Swiss mice. Bull. Environ. Contam. Toxicol. 26(4): 508-512.

Baker, M.T., R.M. Nelson and R.A. Van Dyke. 1985. The formation of chlorobenzene and benzene by the reductive metabolism of lindane in rat liver microsomes. Arch. Biochem. Biophys. 236(2): 506-514. [CA 102(13):107833a]

Bakthavathsalam, R. and Y.S. Reddy. 1981. Survival growth of the fish Anabas testudineus (Bloch) exposed to lindane. Indian J. Environ. Health. 23(4): 270-274.

Baquar, S.R. and N.R. Kahn. 1971. Effect of γ-HCH on the mitotic cells of Pisum sativum L. Rev. Biol. (Lisbon). 7: 195-202.

Barros, S.B. and A.M. Saliba. 1978. Toxicity of the hexachlorocyclohexane in rats. Toxicology. 10(3): 271-279.

Barros, S.B.M., K. Simizu and V.B.C. Junqueira. 1982. Renal and hepatic acid and alkaline phosphatases activity during experimental technical hexachlorocyclohexane poisoning. An. Farm. Quim. Sao Paulo. 22: 11-17. (Por.) (Taken from IAP/84/07444)

Basha, S.M., K.S.P. Rao, K.R.S.S. Rao and K.V.R. Rao. 1983. Differential toxicity of malathion, BHC and carbaryl to the freshwater fish, Tilapia mossambica (Peters). Bull. Environ. Contam. Toxicol. 31(5): 543-546.

Basha, S.M., K.S.P. Rao, K.R.S.S. Rao and K.V.R. Rao. 1984. Respiratory potentials of the fish (Tilapia mossambica) under malathion, carbaryl and lindane intoxication. Bull. Environ. Contam. Toxicol. 32(5): 570-574.

Baumann, K., J. Angerer, R. Heinrich and G. Lehnert. 1980. Occupational exposure to hexachlorocyclohexane. I. Body burden of HCH-isomers. Int. Arch. Occup. Environ. Health. 47: 119-127. (Cited in U.S. EPA, 1985a)

Benes, V. and R. Sram. 1969. Mutagenic activity of some pesticides in Drosophila melanogaster. Ind. Med. 38: 50-52.

Bevenue, A., J.W. Hylin, Y. Kawano and T.W. Kelley. 1972. Organochlorine pesticide residues in water, sediment, algae and fish, Hawaii--1970-1971. Pest. Monit. J. 6: 56-64.

Bhatt, D.K., S.K. Nigam, B.C. Lakkad, et al. 1981. Sequential histochemical changes in the distribution of alkaline phosphatase in BHC-induced liver tumors in pure inbred Swiss mice. Cell Mol. Biol. 27(2-3): 231-238.

Bluzat, R. and J. Seuge. 1979. Effects of three insecticides (lindane, fenthion, and carbaryl) on the acute toxicity to four aquatic invertebrate species and the chronic toxicity to the pulmonate mollusc Lymnea. Environ. Pollut. 18(1): 51-70.

Borghi, H., S. Puiseux-Dao, S. Bonotto and D. Hoursiangou-Neubrun. 1973. Effects of lindane on Acetabularia mediterranea. Protoplasma. 78(1-2): 99-112.

Boulekbache, H. and C. Spiess. 1974. Effect of lindane on trout fry (Salmo irideus Gibb). Changes in glycolytic enzymes. Bull. Soc. Zool. Fr. 99(1): 79-85. (Taken from PESTAB/76/1492)

Brooksbank, P. 1983. The Canadian Network for Sampling Organic Compounds in Precipitation. Environment Canada, Inland Waters Directorate, Water Quality Branch Tech. Bull. No. 129.

Buselmaier, W., G. Rohrborn and P. Propping. 1972. Mutagenicity investigating with pesticides in the host-mediated assay and the dominant-lethal test in mice. Biol. Zbl. 91: 311-325. (Cited in IARC, 1979)

Butler, P.A. 1963. Commercial fisheries investigations, pesticide-wildlife studies: A review of Fish and Wildlife Service investigations during 1961-1962. USDI Fish Wildl. Circ. 167: 11. (Cited in U.S. EPA, 1980b)

Butler, P.A. 1967. Pesticide residues in estuarine mollusks. In: Proc. of the Natl. Symp. Estuarine Pollution., Stanford Univ., Dept. of Civil Engineering, Stanford, CA. (Cited in U.S. EPA, 1971)

Calabrese, A. 1971. Effects of some pollutants on embryos and larvae of the American oyster and hard shell clam. Am. Chem. Soc. Div. Water, Air Waste Chem., Gen. Pap. 11(2): 64-75. [CA 79(7):39068j]

Canton, J.H. and W. Slooff. 1977. The usefulness of *Lymnaea stagnalis* L. as a biological indicator in toxicological bio-assays (model substance α-HCH). Water Res. 11(1): 117-121.

Canton, J.H., P.A. Greve, W. Slooff and G.J. Van Esch. 1975. Toxicity, accumulation, and elimination studies of α-hexachlorocyclohexane (α-HCH with freshwater organisms of different trophic levels. Water Res. 9(12): 1163-1169.

Canton, J.H., G.J. Van Esch, P.A. Greve and A.B.A.M. Van Hellemond. 1977. Accumulation and elimination of γ-hexachlorocyclohexane (γ-HCH) by the marine algae Chlamydomonas and Dunaliella. Water Res. 11(1): 111-115.

Canton, J.H., R.C.C. Wegman, T.J.A. Vulto, C.H. Verhoef and G.J. Van Esch. 1978. Toxicity, accumulation and elimination studies of α-hexachlorocyclohexane with saltwater organisms of different trophic levels. Water Res. 12(9): 687-690.

Castro, T.F. and T. Yoshida. 1974. Effect of organic matter on the biodegradation of some organochlorine insecticides in submerged soils. Soil Sci. Plant Nutr. 20: 363-370.

Ceschini, P. and R. Chauchaix. 1980. Transfer of organochlorine pesticide residues into cigarette smoke as a function of tobacco blends and filter types. Beitr. Tabakforsch. 19(2): 134-138. (Taken from PESTAB/81/0381)

Chadwick, R.W. and J.J. Freal. 1972. Identification of five unreported lindane metabolites recovered from rat urine. Bull. Environ. Contam. Toxicol. 7(2-3): 137-146.

Chadwick, R.W., L.T. Chuang and K. Williams. 1975. Dehydrogenation, a previously unreported pathway of lindane metabolism in mammals. Pestic. Biochem. Physiol. 5(6): 575-586.

Chadwick, R.W., M.F. Copeland and C.J. Chadwick. 1978a. Enhanced pesticide metabolism, a previously unreported effect of dietary fibre in mammals. Food Cosmet. Toxicol. 16(3): 217-225.

Chadwick, R.W., C.C. Bryden, M.F. Copeland, J.J. Freal and S.W. Sovocool. 1978b. The identification of three previously unreported lindane metabolites from mammals. Chemosphere. 7(8): 633-640.

Chadwick, R.W., E.J. Faeder, L.C. King, M.F. Copeland, K. Williams and L.T. Chuang. 1978c. Effect of acute and chronic Cd exposure on lindane metabolism. Ecotoxicol. Environ. Saf. 2: 301-316. (Cited in U.S. EPA, 1985a)

Chand, B. and M. Ramachandran. 1980. Effect of dietary hexachlorocyclohexane on certain biochemical changes in rats. Ind. J. Exp. Biol. 18: 735-736. (Cited in U.S. EPA, 1985a)

Chernoff, N. and R.J. Kavlock. 1983. A teratology test system which utilizes postnatal growth and viability in the mouse. Environ. Sci. Res. 27: 417-427.

Chin, E. and D.M. Allen. 1957. Toxicity of an insecticide to two species of shrimp, Penaeus aztecus and Penaeus setiferis. Texas J. Sci. 9: 270. (Cited in U.S. EPA, 1980b)

Chin, Y.N. and K.I. Sudderuddin. 1979. Effect of methamidophos on the growth rate and esterase activity of the common carp Cyprinus carpio L. Environ. Pollut. 18(3): 213-220.

Chiou, C.T., V.H. Freed, L.J. Peters and R.L. Khonert. 1980. Evaporation of solutes from water. Environ. Int. 3(3): 231-236.

Chovelon, A., L. Geoger, C. Gulayets, et al. 1984. Pesticide and PCB levels in fish from Alberta (Canada). Chemosphere. 13(1): 19-32.

Cole, R.H., R.E. Frederick, R.P. Healy and R.G. Rolan. 1984. Preliminary findings of the priority pollutant monitoring project of the Nationwide Urban Runoff Program. J. Water Pollut. Control Fed. 56: 898-908.

Colson, J.G. 1979. Benzene hexachloride. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 5, 3rd ed., M. Grayson and D. Eckroth, Ed. John Wiley and Sons, Inc., New York. p. 808-818.

Cope, O.B. 1965. Sport fishery investigation. In: Effects of Pesticide in Fish and Wildlife, 1964 Research Findings of the Fish and Wildlife Service. U.S. Fish Wildl. Serv., Circ. 226. p. 51-63. (Cited in U.S. EPA, 1971)

Cope, O.B. 1966. Contamination of the freshwater ecosystem by pesticide. J. Appl. Ecol. 3: 33-44. (Cited in Pimentel, 1971; U.S. EPA, 1971)

Culley, D.D., Jr. and D.E. Ferguson. 1969. Patterns of insecticide resistance in the mosquitofish, Gambusia affinis. J. Fish. Res. Board Can. 26: 2395-2401.

Czegledi-Janko, G. and P. Avar. 1970. Occupational exposure to lindane: Clinical and laboratory findings. Br. J. Ind. Med. 27(3): 283-286.

Das, B. and P.K. Singh. 1977. Detoxication of the pesticide benzene-hexachloride by blue-green algae. Microbiol. Lett. 4(14): 99-102.

Davis, H.C. and H. Hidu. 1969. Effects of pesticides on embryonic development of clams and oysters and on survival and growth of the larvae. Fish. Bull. 67(2): 383-404. (Cited in U.S. EPA, 1972)

DeBrabander, M., R. Van deVeire, F. Aerts, S. Geuens and J. Hoebeke. 1976. A new culture model facilitating rapid quantitative testing of mitotic spindle inhibition in mammalian cells. J. Natl. Cancer Inst. 56: 357-363. (Cited in U.S. EPA, 1985a)

Deo, P.G., S.B. Hasan and S.K. Majumder. 1980. Isomerization of beta-HCH in aqueous solution. J. Environ. Sci. Health B. 15(2): 147-164.

Desi, I. 1974. Neurotoxicological effect of small quantities of lindane. Int. Arch. Arbeitsmed. 33: 153-162. (Cited in U.S. EPA, 1985a)

Desi, I., L. Varga and I. Farkas. 1978. Studies on the immunosuppressive effect of organochlorine and organophosphoric pesticides in subacute experiments. J. Hyg. Epidemiol. Microbiol. Immunol. (Praha). 22(1): 115-122. (Cited in U.S. EPA, 1985a)

Dewan, A., S.K. Gupta, J.P. Jani and S.K. Kashyap. 1980. Effects of lindane on antibody response to typhoid vaccine in weanling rats. J. Environ. Sci. Health. [B]. 15(4): 395-402. (Cited in U.S. EPA, 1985a)

Dikshith, T.S.S. and K.K. Datta. 1977. Comparative response of male rat to parathion and lindane individually and in a mixture. In: Proc. Int. Symp. Ind. Toxicol. Environ. Pollut. Human Health. p. 631-737.

Dikshith, T.S.S., S.K. Tandon, K.K. Datta, P.K. Gupta and J.R. Behari. 1978. Comparative response of male rats to parathion and lindane: Histopathological and biochemical studies. Environ. Res. 17(1): 1-9.

Di Toro, D.M. and P.R. Paquin. 1984. Time variable model of the fate of DDE and lindane in a quarry. Environ. Toxicol. Chem. 3(2): 335-353.

Dive, D., H. Leclerc and G. Personne. 1980. Pesticide toxicity on the ciliate protozoan Colpidium campylum: Possible consequences of the effect of pesticides in the aquatic environment. Ecotoxicol. Environ. Saf. 4(2): 129-133.

Doelman, P., L. Haanstra, E. De Ruiter and J. Slange. 1985. Rate of microbial degradation of high concentrations of alpha-PHC in soil under aerobic and anaerobic conditions. Chemosphere. 14(5): 565-570.

Duggan, R.E., P.E. Corneliussen, M.B. Duggan, B.M. McMahon and R.J. Martin. 1983. Pesticide Residue Levels in Foods in U.S. from July 1, 1969 to June 30, 1976. Food and Drug Administration and Association of Official Analytical Chemists Publication.

Duinker, J.C. and M.T.J. Hillebrand. 1979. Behavior of PCB, pentachlorobenzene, hexachlorobenzene, alpha-HCH, gamma-HCH, beta-HCH, dieldrin, endrin and P,P'-DDD in the Rhine-Meuse estuary and the adjacent coastal area. Neth. J. Sea Res. 13: 256-281.

Dzierzawski, A. 1977. Embryotoxicity studies of lindane in the golden hamster, rat and rabbit. Bull. Vet. Inst. Pulawy. 21(3-4): 85-93. (Cited in U.S. EPA, 1985a)

Earl, F.L., E.J. Van Loon, B.E. Melveger, et al. 1970. Lindane toxicity. A comparative study in dogs and miniature swine with and without phenobarbital. Toxicol. Appl. Pharmacol. 17: 287. (Cited in U.S. EPA, 1985a)

Eichler, D., W. Heupt and W. Paul. 1983. Comparative study on the distribution of α-BHC and γ-BHC in the rat with particular reference to the problem of isomerization. Xenobiotica. 13(11): 639-648.

Eisenreich, S.J., B.B. Looney and J.D. Thornton. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ. Sci. Technol. 15(1): 30-38.

Eisler, R. 1969. Acute toxicities of insecticides to marine decapod crustaceans. Crustaceana. 16(3): 302-310. (Cited in U.S. EPA, 1972, 1980b; Pimentel, 1971)

Eisler, R. 1970a. Acute toxicities of organochlorine and organophosphorus insecticides to estuarine fishes. Bureau of Sport Fish. Wildl., Tech. Paper 46. Government Printing Office, Washington, DC. 12 p.

Eisler, R. 1970b. Factors affecting pesticide-induced toxicity in an estuarine fish. Bureau of Sport Fish. Wildl., Tech. Paper 45. Government Printing Office, Washington, DC. 20 p.

El Beit, I.O.D., J.V. Wheelock and D.E. Cotton. 1981. Pesticide-microbial interaction in the soil. Int. J. Environ. Studies. 16: 189-196.

Elezovic, I. and V. Mitrovic-Tutundzic. 1981. Acute toxicity of DDT, lindane, and heptachlor in water on carp (*Cyprinus carpio* L.) fry. Vodoprivreda. 13(73): 367-370. (Ser.) [CA 96(3):15837j]

Engst, R., R.M. Macholz, M. Kujawa, H.J. Lewerenz and R. Plass. 1976. The metabolism of lindane and its metabolites γ-2,3,4,5,6-pentachlorocyclohexene, pentachlorobenzene, and pentachlorophenol in rats and the pathways of lindane metabolism. J. Environ. Sci. Health, Part B. B11(2): 95-117.

Engst, R., R.M. Macholz and M. Kujawa. 1979. Recent state of lindane metabolism. Part II. Residue Rev. 72: 71-95.

Ernst, W. 1975. Absorption, secretion and metabolism of lindane-^{14}C by *Mytilus edulis*. Chemosphere. 4(6): 375-380.

Ernst, W. 1977. Determination of the bioconcentration potential of marine organisms -- A steady state approach. I. Bioconcentration data for seven chlorinated pesticides in mussles (*Mytilus edulis*) and their relation to solubility data. Chemosphere. 6(11): 731-740.

Escoubet, P. 1978. Effects of lindane on cultures of marine phytoplanktonic algae and cockles. Preliminary results. Rev. Int. Oceanogr. Med. 49: 21-27. (Fre.) [CA 88(25):184243c]

Falandysz, J. 1982. Chlorinated hydrocarbons in salmon netted in Gdansk Bay, Baltic Sea (Poland). Meeresforschung. 29(4): 219-224. (Taken from HEEP/83/12814)

Falandysz, J. 1984. Organochlorine pesticides and polychlorinated biphenyls in livers of cod (Gadus morhua) from the southern Baltic, 1981. Z. Lebensm-Unters -Forsch. 179(4): 311-314. (Taken from HEEP/85/05140)

Federal Register. 1983. Intent to cancel pesticide products containing lindane; denial of applications for registration of pesticide products containing lindane; determination concluding the Rebuttable Presumption Against Registration; availability of position document. 48 FR 48512.

Fitzgerald, G.P., G.C. Gerloff and F. Skoog. 1952. Stream pollution: Studies on chemicals with selective toxicity to blue-green algae. Sewage Ind. Wastes. 24(7): 888-896.

Fitzhugh, O.G., A.A. Nelson and J.P. Frawley. 1950. The chronic toxicities of technical benzene hexachloride and its alpha, beta and gamma isomers. J. Pharmacol. Exp. Therap. 100: 59-66.

Fitzloff, J.F. and J.C. Pan. 1984. Epoxidation of the lindane metabolite, B-PCCH, by human- and rat-liver microsomes. Xenobiotica. 14(7): 599-604.

Fitzloff, J.F., J. Portig and K. Stein. 1982. Lindane metabolism by human and rat liver microsomes. Xenobiotica. 12(3): 197-202.

Foulquier, L., A. Reynier, A. Grauby and P. Bovard. 1971. Toxicity of lindane to eels (Anguilla Anguilla L.) Compt. Rend. Acad. Agr. France. 57(12): 1060-1068. (Fre.) (Taken from HAPAB/72/02196)

Frawley, J P. and O.G. Fitzhugh. 1949. Rate of disappearance of isomers of benzene hexachloride from fat deposits in rats. Fed. Proc. 8: 292-293.

Freal, J.J. and W.R. Chadwick. 1973. Metabolism of hexachlorocyclohexane to chlorophenols and effect of isomer pretreatment on lindane metabolism in rat. J. Agric. Food Chem. 21(3): 424-427.

Freimane, T. and M. Grundule. 1976. Quantitative shifts of lipid fractions in carp under the effect of lindane and DDT. Eksp. Vodn. Toksikol. 6: 248-254. [CA 88(19):131674n]

Frisque, G.E., M. Galous and A. Bernes. 1983. Accumulation of two trace pollutants (polychlorobiphenyls and γ-HCH) in aquatic bryophytes of the Meuse River. Meded. Fac. Landbouwwet., Rijksuniv. Gent. 48(4): 971-983. [CA 100(5):30637p]

Gaeta, S.A., N. Kadekaru, N. Pereira and L.R. Tommasi. 1983. Preliminary observations on the toxicity of γ-HCH and mercury(II) chloride to Artemia salina. Bol. Inst. Oceanogr. (Univ. Sao Paulo). 32(1): 21-31. (Por.) [CA 102(11):91089z]

Geyer, H., P. Sheehan, D. Kotzias, D. Freitag and F. Korte. 1982. Prediction of ecotoxicological behavior of chemicals: Relationship between physicochemical properties and bioaccumulation of organic chemicals in the mussel Mytilus edulis. Chemosphere. 11(11): 1121-1134.

Glotfelty, D.E., A.W. Taylor, B.C. Turner and W.H. Zoller. 1984. Volatilization of surface-applied pesticides from fallow soil. J. Agric. Food Chem. 32: 638-644.

Gopalaswamy, U.V. and A.S. Aiyar. 1984. Biotransformation of lindane in the rat. Bull. Environ. Contam. Toxicol. 32(2): 148-156.

Goto, M., M. Hattori, T. Miyagawa and M. Enomoto. 1972. Ecological Chemistry. II. Hepatoma formation in mice after administration of high doses of hexachlorocyclohexane isomers. Chemosphere. 1(6): 279-282. (Ger.)

Gray, L.E., Jr. and R.J. Kavlock. 1984. An extended evaluation of an in vivo teratology screen utilizing postnatal growth and viability in the mouse. Teratog. Carcinog. Mutagen. 4(5): 403-426.

Grey, W.E., D.E. Marthre and S.J. Rogers. 1983. Potential exposure of commercial seed-treating applicators to the pesticides carboxin-thiram and lindane. Bull. Environ. Contam. Toxicol. 31(2): 244-250.

Grover, P.L. and P. Sims. 1965. The metabolism of 2,3,4,5,6-pentachlorocyclohex-1-ene and hexachlorocyclohexane in rats. Biochem. J. 96: 521. (Cited in U.S. EPA, 1980a)

Gupta, P.K., V.S. Mujumdar and P.S. Rao. 1984. Studies on the toxicity of some insecticides to a freshwater teleost *Lebistes reticulatus* (Peters). Acta Hydrochim. Hydrobiol. 12(6): 629-636.

Haider, K. 1979. Degradation and metabolization of lindane and other hexachlorocyclohexane isomers by anaerobic and aerobic soil microorganisms. Z. Naturforsch. Teil C. 34(11): 1066-1069.

Haines, T.A. 1983. Organochlorine residues in brook trout (*Salvelinus fontinalis*) from remote lakes in the northeastern USA. Water Air Soil Pollut. 20(1): 47-54.

Hamelink, J.L. and R.C. Waybrant. 1976. DDE and lindane in a large-scale model lentic ecosystem. Trans. Am. Fish. Soc. 105: 124-134.

Hanada, M., C. Yutani and T. Miyaji. 1973. Induction of hepatoma in mice by benzene hexachloride. Gann. 64: 511-513.

Hansen, P.D. 1979. Experiments on the accumulation of lindane (γ-BHC) by the primary producers *Chlorella* spec. and *Chlorella pyrenoidosa*. Arch. Environ. Contam. Toxicol. 8(6): 721-731.

Hansen, P.D. 1980. Uptake and transfer of the chlorinated hydrocarbon lindane (γ-BHC) in a laboratory freshwater food chain. Environ. Pollut. (Series A). 21(2): 97-108.

Hartley, D.M. and J.B. Johnston. 1983. Use of the freshwater clam Corbicula manilensis as a monitor for organochlorine pesticides. Bull. Environ. Contam. Toxicol. 31: 33-40.

Hashimoto, Y. and Y. Nishiuchi. 1981. Establishment of bioassay methods for the evaluation of acute toxicity of pesticides to aquatic organisms. J. Pest. Sci. 6(2): 257-264.

Hawley, G.G., Ed. 1981. The Condensed Chemical Dictionary, 10th ed. Van Nostrand Reinhold Co., New York. p. 526.

Henderson, C., Q.H. Pickering and C.M. Tarzwell. 1959. Relative toxicity of ten chlorinated hydrocarbon insecticides to four species of fish. Trans. Am. Fish. Soc. 88: 23-32.

Herbst, M. and G. Bodenstein. 1972. Toxicology of lindane. In: Lindane, E. Ulmann, Ed. Verlag K. Shillinger Publ. Freiburg im Breisgaw. p. 23-82. (Cited in U.S. EPA, 1980a, 1985a)

Herbst, M., I. Weisse and H. Koellmer. 1975. Possible hepatocarcinogenic effects of lindane. Toxicology. 4(1): 91-96.

Herzberg, A., A. Gelman and A.S. Perry. 1980. The location of lindane (γ-hexachlorocyclohexane) in fish after deliberate poisoning. Bamidgeh (Bull. Fish Cult. Israel). 32(1): 16-19. (Taken from PESTAB/81/0750)

Hill, D.W. and P.L. McCarty. 1976. Anaerobic degradation of selected chlorinated hydrocarbon pesticides. J. Water Pollut. Control Fed. 39: 1259-1277.

Hitachi, M., K. Yamada and S. Takayama. 1975. Cytologic changes induced in rat liver cells by short-term exposure to chemical substances. J. Natl. Cancer Inst. 54: 1245-1247. (Cited in IARC, 1979)

IARC (International Agency for Research on Cancer). 1979. IARC Monograph on the Evaluation of Carcinogenic Risk of Chemicals to Humans. Hexachlorocyclohexane (technical HCH and lindane). IARC, WHO, Lyon, France. Vol. 20, p. 195-239.

Inman, C.B.E. and A.P.M. Lockwood. 1977. Some effects of methylmercury and lindane on sodium regulation in the amphipod Gammarus duebeni during changes in the salinity of its medium. Comp. Biochem. Physiol. 58C: 67-75.

Ishidate, M., Jr. and S. Odashima. 1977. Chromosome tests with 134 compounds on Chinese hamster cell in vitro -- A screening for chemical carcinogens. Mutat. Res. 48: 337-354.

Ito, N., H. Hagasaki, M. Arai, S. Sugihara and S. Makiura. 1973a. Histologic and ultrastructural studies on the hepatocarcinogenicity of benzene hexachloride in mice. J. Natl. Cancer Inst. 51(3): 817-826.

Ito, N., H. Nagasaki, M. Aria, et al. 1973b. Histopathologic studies on liver tumorigenesis induced in mice by technical polychlorinated biphenyls and its promoting effect on liver tumors induced by benzene hexachloride. J. Natl. Cancer Inst. 51(5): 1637-1646.

Ito, N., H. Nagasaki, H. Aoe, et al. 1975. Brief communication: Development of hepatocellular carcinomas in rats treated with benzene hexachloride. J. Natl. Cancer Inst. 54: 801-805.

Ito, N., M. Hananouchi, S. Sugihara, et al. 1976. Reversibility and irreversibility of liver tumors in mice induced by the α-isomer of 1,2,3,4,5,6-hexachlorocyclohexane. Cancer Res. 36(7, Pt. 1): 2227-2234.

Jeanne, N. 1979. Effects of lindane on the division, cell cycle and biosynthesis of two unicellular algae. Can. J. Bot. 57(13): 1464-1472.

Jenssen, D. and C. Ramel. 1980. The micronucleus test as part of a short-term mutagenicity test program for the prediction of carcinogenicity evaluated by 143 agents tested. Mutat. Res. 75: 191-202.

Johnson, W.W. and M.J. Finley. 1980. Handbook of acute toxicity of chemicals to fish and aquatic invertebrates. U.S. Dept. of Interior, Fish and Wildl. Serv., Washington, DC. Res. Publ. 173.

Joshi, A.G. and M.S. Rege. 1980. Acute toxicity of some pesticides and a few inorganic salts to the mosquito fish Gambusia affinis (Baird and Girard). Indian J. Exp. Biol. 18(4): 435-437.

Juarez, A. and J.A. Guzman. 1984. Chronic effect of five organochlorine insecticides on larvae of *Bufo arenarum* (H). Commun. Biol. 2(4): 411-415. (CA 101:224365q)

Kaiser, K.L.E. 1982. Early determination of organochlorine contamination from residue ratios in the sea lamprey (*Petromyzon marinus*) and its lake whitefish (*Coregonum clupeaformis*) host. Can. J. Fish. Aquat. Sci. 39: 571-579.

Kanazawa, J. 1981. Measurement of the bioconcentration factors of pesticides by freshwater fish and their correlation with physicochemical properties or acute toxicities. Pestic. Sci. 12(4): 417-424.

Kanazawa, J. 1982. Relationship between the molecular weights of pesticides and their bioconcentration factors by fish. Experientia. 38(9): 1045-1046.

Kanazawa, J. 1983. A method of predicting the bioconcentration potential of pesticides by using fish. JARQ. 17: 173-179.

Kar, S. and P.K. Singh. 1979. Effect of nutrients on the toxicity of pesticides carbofuran and hexachlorocyclohexane to blue-green alga *Nostoc muscorum*. Z. Allg. Mikrobiol. 19(7): 467-472.

Kashyap, S.K., S.K. Nigam, R.C. Gupta, A.B. Karnik and S.K. Chatterjee. 1979. Carcinogenicity of hexachlorocyclohexane (BHC) in purebred Swiss mice. J. Environ. Sci. Health, Part B. B14(3): 305-318.

Katz, M. 1961. Acute toxicity of some organic insecticides to three species of salmonids and to the three-spine stickleback. Trans. Am. Fish. Soc. 90(3): 264-268.

Kaur, K. and S. Kirk. 1983. Effect of BHC and sumithion on ovarian recrudescence in common carp, Cyprinus carpio. Indian J. Ecol. 19(2): 182-187.

Keith, L.H., W.A. Garrison, F.R. Allen, et al. 1976. Identification of organic compounds in drinking water from thirteen U.S. cities. In: Identification and Analysis of Organic Pollutants in Water, L.H. Keith, Ed. Ann Arbor Science, Ann Arbor, MI. p. 329-373.

Kenaga, E.E. 1980. Predicted bioconcentration factors and soil sorption coefficients of pesticides and other chemicals. Ecotoxicol. Environ. Saf. 4: 26-38.

Khamidov, M.K. 1984. Experimental study of the effect of industrial grade hexachloran on pregnancy and physical development of the progeny in 3 generations. Med. Zh. Uzb. 5: 57-60. (Russ.) [CA 101(21):185619d]

Khera, K.S., C. Whalen, G. Trivett and G. Angers. 1979. Teratogenicity studies on pesticidal formulations of dimethoate, diuron and lindane in rats. Bull. Environ. Contam. Toxicol. 224(4-5): 522-529.

Kiraly, J., I. Szentesi, M. Ruzicaka and A. Czeire. 1979. Chromosome studies in workers producing organophosphate insecticides. Arch. Environ. Contam. Toxicol. 8: 309-319. (Cited in U.S. EPA, 1985a)

Kitamura, S., D. Sumino and K. Hayakawa. 1970. No title provided. Japan J. Publ. Health. 17: 108-112. (Cited in U.S. EPA, 1980a, 1985a)

Kohnen, R., K. Haider and G. Jagnow. 1975. Investigations on the microbial degradation of lindane in submerged and aerated moist soil. Environ. Qual. Saf. Suppl. 3: 223-236.

Konasewich, D., W. Traversy and H. Zar. 1978. Great Lakes Water Quality. Status Report on Organic and Heavy Metal Contaminants in the Lakes Erie, Michigan, Huron and Superior Basins. Implementation Committee of the Great Lakes Water Quality Board, Windsor, Ontario. July.

Kopecek, K., F. Fueller, W. Ratzmann and W. Simonis. 1975. Light dependent insecticide effect on unicellular algae. Ber. Btsch. Bot. Ges. 88(2): 269-281. (Ger.) [CA 84(19):131132b]

Korn, S. and R. Earnest. 1974. Acute toxicity of twenty insecticides to striped bass, Morone saxatilis. Calif. Fish Game. 60: 128-131.

Kraybill, H.F. 1977. Global distribution of carcinogenic pollutants in water. Ann. N.Y. Acad. Sci. 298: 80-89.

Krishnakumari, M.K. 1977. Sensitivity of the alga Scenedesmus acutus to some pesticides. Life Sci. 20: 1525-1532.

Kujwa, M., R. Engst and R. Macholz. 1977. On the metabolism of lindane. In: Proc. In. Symp. Environ. Pollut. Human Health. p. 661-672. (Cited in U.S. EPA, 1980a, 1985a)

Kuntz, K.W. and N.D. Warry. 1983. Chlorinated organic contaminants in water and suspended sediments of the lower Niagara river. J. Great Lakes Res. 9: 281-286.

Kurihara, N., K. Tanaka and M. Nakajima. 1979. Mercapturic acid formation from lindane in rats. Pestic. Biochem. Physiol. 10: 137-150. (Cited in U.S. EPA, 1980a, 1985a)

Kutz, F.W., A.R. Yobs and H.S.C. Yang. 1976. National Pesticide Monitoring Programs. In: Air Pollution from Pesticides and Agricultural Processes, R.E. Lee, Jr., Ed. CRC Press, Cleveland, OH. p. 95-137.

Lakkad, B.C., S.K. Nigam, A.B. Karnik, et al. 1982. Dominant-lethal study of technical-grade hexachlorocyclohexane in Swiss mice. Mutat. Res. 101(4): 314-320.

Lakshmanan, F.L., A Pommer and O. Patterson. 1979. Chlorinated hydrocarbon insecticide residues in tissues of rats before and after reduction of body fat by dietary restriction. J. Agric. Food Chem. 27(4): 720-725. (Cited in U.S. EPA, 1980a, 1985a)

Laug, E.P. 1948. Tissue distribution of a toxicant following oral ingestion of the γ-isomer of benzene hexachloride by rats. J. Pharmacol. Exp. Ther. 93: 277-281.

Lawlor, T., S.R. Haworth and P. Voytek. 1979. Evaluation of the genetic activity of nine chlorinated phenols, seven chlorinated benzenes and three chlorinated hexanes. Environ. Mutagen. 1: 143. (Cited in U.S. EPA, 1985a)

Leatherland, J.F. and R.A. Sonstegard. 1982. Bioaccumulation of organochlorines by yearling coho salmon (Oncorhynchus kisutch Walbaum) fed diets containing Great Lakes coho salmon, and the pathophysiological responses of the recipients. Comp. Biochem. Physiol. C. 72C(1): 91-99.

Lehman, A.J. 1952a. Chemicals in foods: A report to the Association of Food and Drug Officials on current development. Part II. Pesticides. Section IV. Biochemistry. U.S. Assoc. Food Drug Office Quart. Bull. 16: 85-91. (Cited in U.S. EPA, 1980a, 1985a)

Lehman, A.J. 1952b. Chemicals in foods: A report to the Association of Food and Drug Officials on current developments. Part II. Pesticides. Section V. Pathology. U.S. Assoc. Food Drug Office Quart. Bull. 16: 126-132. (Cited in U.S. EPA, 1980a, 1985a)

Lehman, A.J. 1965. Summaries of pesticide toxicity. Part I. Chlorinated organic compounds. Assoc. of Food and Drug Officials of the United States, Topeka, KS. p. 27-29. (Cited in U.S. EPA, 1985a)

Lewis, R.G. and R.E. Lee, Jr. 1976. Air pollution from pesticides sources, occurrence and dispersion. In: Air Pollution from Pesticides and Agricultural Processes. CRC Press. p. 5-51.

Lichtenstein, E.P., T.W. Fuhremann and K.R. Schulz. 1971. Persistence and vertical distribution of DDT, lindane and aldrin residues, ten and fifteen years after a single soil application. J. Agric. Food Chem. 19: 713-721.

Liu, P.T.Y. 1982. The role of genetic factors and route of administration on the metabolic disposition of lindane in mice. Dissert. Abstr. 43B: 1049. (Cited in U.S. EPA, 1985a)

Lyman, W.J., W.F. Reehl and D.H. Rosenblatt. 1982. Handbook of Chemical Property Estimation Methods. McGraw-Hill Book Co., New York. p. 2-14, 4-9, 15-11, 15-24.

Macek, K.J. and W.A. McAllister. 1970. Insecticide susceptibility of some common fish family representatives. Trans. Am. Fish. Soc. 99(1): 20-27

Macek, K.J., C. Hutchinson and O.B. Cope. 1969. The effects of temperature on the susceptibility of bluegills and rainbow trout to selected pesticides. Bull. Environ. Contam. Toxicol. 4: 174-183.

Macek, K.J., et al. 1976. Chronic toxicity of lindane to selected aquatic invertebrates and fishes. U.S. EPA, Duluth, MN. EPA-600/3-76-046. (Cited in U.S. EPA, 1980b)

Macholz, R.M., R. Knoll, H.J. Lewerenz, M. Petrzika and R. Engst. 1982a. Metabolism of α-hexachlorocyclohexane. Free metabolites in urine and organs of rats. Xenobiotica. 12(4): 227-231.

Macholz, R.M., R. Knoll, H.J. Lewerenz and R. Plass. 1982b. Biodegradation of beta-hexachlorocyclohexane. Free metabolites in rat urine and organs. Arch. Toxicol. 50: 85-88.

Mackay, D. and P.J. Leinonen. 1975. Rate of evaporation of low-solubility contaminants from water bodies to atmosphere. Environ. Sci. Technol. 9: 1178-1180.

MacRae, I.C., Y. Yamaya and T. Yoshida. 1984. Persistence of hexachlorocyclohexane isomers in soil suspensions. Soil Biol. Biochem. 16: 285-286.

Madhu, C., K.J. Rao and K.V.R. Rao. 1984. Hematological changes in Sarotherodon mossambicus exposed to lindane. J. Food Sci. Technol. 21(1): 53-55. [CA 101(11):85266t]

Maity, A.K. and J. Saxena. 1979. Effects of BHC on a freshwater species of Daphnia (Daphnia carinata King). Natl. Acad. Sci. Lett. (India). 2(3): 113-114. [CA 91(11):84650b]

Malaiyandi, M., S.M. Shah and P. Lee. 1982. Fate of alpha-BHC and gamma-BHC isomers under simulated environmental conditions. J. Environ. Sci. Health Part A Environ. Sci. Eng. 17(3): 283-298.

Marcelle, C. and J.P. Thome. 1983. Acute toxicity and bioaccumulation of lindane in gudgeon, *Gobio gobio* (L). Bull. Environ. Contam. Toxicol. 31(4): 453-458.

Marcelle, C. and J.P. Thome. 1984. Relative importance of dietary and environmental sources of lindane in fish. Bull. Environ. Contam. Toxicol. 33(4): 423-429.

Marchal-Segault, D. 1982. Effects of lindane, an organochloride insecticide, on the thyroid of *Xenopus laevis* Daudin larvas in premetamorphic stages. C.R. Seances Soc. Biol. Ses Fil. 176(6): 839-848. (Fre.) [CA 98(21):174399a]

Marchal-Segualt, D. and F. Ramade. 1981. The effects of lindane, an insecticide, on hatching and postembryonic development of *Xenopus laevis* (Daudin) anuran amphibian. Environ. Res. 24(2): 250-259.

Martin, D.B. and W.A. Hartman. 1985. Organochlorine pesticides and polychlorinated biphenyls in sediment and fish from wetlands in the north central United States. J. Assoc. Off. Anal. Chem. 68(4): 712-717.

Mathur, S.P. and J.B. Saha. 1975. Microbial degradation of lindane ^{14}C in a flooded sandy loam soil. Soil Sci. 120: 301-317.

Matsumura, F. and H.J. Benezet. 1973. Studies on the bioaccumulation and microbial degradation of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Environ. Health Perspect. 253-258.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. The Resource Agency of California, State Water Qual. Cont. Board. Publ. 3-A.

McLeay, D.J. 1976. Rapid method for measuring acute toxicity of pulpmill effluents and other toxicants to salmonid fish at ambient room temperature. J. Fish. Res. Board Can. 33: 1303-1311.

Metcalf, R.L., I.P. Kapoor, P.Y. Lu, C.K. Schuth and P. Sherman. 1973. Model of ecosystem studies of the environmental fate of six organochlorine pesticides. Environ. Health Perspect. 4: 35-44.

Meyer, F.P. 1965. The effect of formulation differences on toxicity of benzene hexachloride to golden shiners. In: Proc. 17th Ann. Conf. Southeast Assoc. Game Fish Comm. p. 186-190. (Cited in U.S. EPA, 1971)

Morgan, D.P., E.M. Stockdaly, R.J. Roberts and A.W. Walter. 1980. Anemia associated with exposure to lindane. Arch. Environ. Health. 35(5): 307-310.

Moriya, M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116 (3-4): 185-216.

Morrison, R.T. and R.N. Boyd. 1973. Organic Chemistry, 3rd ed. Allyn and Bacon, Inc., Boston, MA. p. 457-458.

Müller, D., H. Klepel, R.M. Macholz, H.J. Lewerenz and R. Engst. 1981. Electroneurophysiological studies on neurotoxic effects of hexachlorocyclohexane isomers and γ-pentachlorocyclohexane. Bull. Environ. Contam. Toxicol. 27(5): 704-706.

Munir, K.M. and S.V. Bhide. 1984. Deviations in ornithine-related metabolism during hexachlorocyclohexane-induced hepatocarcinogenesis in mice: Evidence for conversion of glutamate to ornithine. Environ. Res. 35(1): 180-187.

Munir, K.M., C.S. Soman and V. Sumati. 1983. Hexachlorocyclohexane-induced tumorigenicity in mice under different experimental conditions. Tumori. 69(5): 383-386.

Muralidhara, M., K. Krishnakumari and S.K. Majumder. 1979. Effects of carriers on the oral toxicity of lindane (pesticide) (γ-BHC) to albino rats. J. Food Sci. Technol. 16: 105-107. (Cited in U.S. EPA, 1985a)

Nagasaki, H. 1973. Chronic toxicity of benzene hexachloride (BHC). Nara Igaku Zasshi. 24(1-2): 1-26. (Jap.). [CA 79(5):28178u]

Nagasaki, H., S. Tomii, T. Mega, M Marugami and N. Ito. 1971. Development of hepatomas in mice treated with benzene hexachloride. Gann. 62: 431. (Cited in IARC, 1979; U.S. EPA, 1980a)

Nagasaki, H., S. Tomii, T. Mega, M. Marugami and N. Ito. 1972a. Hepatocarcinogenic effect of α-, β-, γ-, and δ-isomers of benzene hexachloride in mice. Gann. 63(3): 393.

Nagasaki, H., S. Tomii, T. Mega, M. Marugami and N. Ito. 1972b. Carcinogenicity of benzene hexachloride (BHC). In: Topics in Chemical Carcinogenesis, W. Nakahara, S. Takayama, T. Sugimura and S. Odashima, Ed. Univ. of Tokyo Press, Tokyo. p. 343-353.

Nagasaki, H., H. Kawabata, Y. Miyata, et. al. 1975. Effect of various factors on induction of liver tumors in animals by the α-isomer of benzene hexachloride. Gann. 66: 185-191.

Nair, G.A. 1981. Toxic effects of certain biocides on a fresh water mite, Hydrachna trilobata viets (Arachnida:Hydrachnoidea:Hydrachnidae). J. Environ. Biol. 2(2): 91-96. [CA 97(1):1904n]

Nash, R.G. 1983. Comparative volatilization and dissipation rates of several pesticides from soil. J. Agric. Food Chem. 31(2): 210-217.

NCI (National Cancer Institute). 1977. Bioassay of lindane for possible carcinogenicity. CAS No. 58-89-9. NTIS PB-273480.

Niethammer, K.R., D.H. White, T.S. Baskett and M.W. Sayre. 1984. Presence and biomagnification of organochlorine chemical residues in Oxbow Lakes of northeastern Louisiana. Arch. Environ. Contam. Toxicol. 13(1): 63-74.

Nigam, S.K., B.C. Lakkad, A.B. Karnik, et al. 1979. Effect of hexachlorocyclohexane feeding on testicular tissue of pure inbred Swiss mice. Bull. Environ. Contam. Toxicol. 23(4-5): 431-437.

Nigam, S.K., A.B. Karnik, B.C. Lakkad and H. Venkatakrishna-Bhatt. 1982. Distribution of isomers of BHC and related histopathology of liver in hexachlorocyclohexane (technical grade BCH) fed mice. Arch. Environ. Health. 37(3): 156-158.

Nigam, S.K., K.N. Thakore, A.B. Karnik and B.C. Lakkad. 1984a. Hepatic glycogen, iron distribution and histopathological alterations in mice exposed to hexachlorocyclohexane. Indian J. Med. Res. 79: 571-579.

Nigam, S.K., B.C. Lakkad, A.B. Karnik and K.M. Thakore. 1984b. Ultrastructural changes in liver of mice exposed to hexachlorocyclohexane. Indian J. Exp. Biol. 22(4): 199-204.

Nybom, N. and B. Knutsson. 1947. Investigations on C-mitosis in *Allium cepa*. I. The cytological effect of hexachlorocyclohexane. Hereditas. 33: 220-234. (Cited in IARC, 1979)

Oesch, F., T. Friedberg, M. Herbst, W. Paul, N. Wilhelm and P. Bentley. 1982. Effects of lindane treatment on drug-metabolizing enzymes and liver weight of DVI mice in which it evoked hepatomas and nonsusceptible rodents. Chem.-Biol. Interact. 40(1): 1-14.

Ohisa, N. and M. Yamaguchi. 1978. Degradation of gamma-BHC in flooded soils enriched with peptone. Agric. Biol. Chem. 42: 1983-1987.

Oliver, B.G. and M.N. Charlton. 1984. Chlorinated organic contaminants on settling particulates in the Niagara river vicinity of Lake Ontario. Environ. Sci. Technol. 18: 903-908.

OSHA (Occupational Safety and Health Administration). 1985. Code of Federal Regulations. 29 CFR 1900.1000

Page, G.W. 1981. Comparison of groundwater and surface water for patterns and levels of contamination by toxic substances. Environ. Sci. Technol. 15: 1475-1481.

Palmer, C.M. and T.E. Maloney. 1955. Preliminary screening for potential algicides. Ohio J. Sci. 55(1): 1-8.

Palmer, A.K., D.D. Cozens, E.J.F. Spicer and A.N. Worden. 1978a. Effects of lindane upon reproductive function in a 3-generation study in rats. Toxicology. 10(1): 45-54.

Palmer, A.K., A.M. Bottomley, A.N. Worden, H. Frohberg and A. Bauer. 1978b. Effect of lindane on pregnancy in the rabbit and rat. Toxicology. 9(3): 239-247.

Pankow, J.F., L.M. Isabelle and W.E. Asher. 1984. Trace organic compounds in rain: 1. Sampler design and analysis by adsorption-terminal desorption. Environ. Sci. Technol. 18(5): 310-318.

Parejko, R. and C.L.J. Wu. 1977. Chlorohydrocarbons in Marquette Fish Hatchery lake trout (Salvelinus namaycush). Bull. Environ. Contam. Toxicol. 17(1): 90-97.

Parejko, R., R. Johnston and R. Keller. 1975. Chlorohydrocarbons in Lake Superior lake trout (Salvelinus namaycush). Bull. Environ. Contam. Toxicol. 14(4): 480-488.

Parker, J.G. 1984. The effects of selected chemicals and water quality on the marine polychaete Ophryotrocha diadema. Water Res. 18(7): 865-868.

Pawar, K.R. and M. Katdare. 1983. Toxicity of Sumithion, BHC and Furadan to the tadpoles of the frog Microhyla ornata. Indian J. Environ. Health. 25(3): 214-217. [CA 100(9):63178t]

Petescu, S., V. Dobre, M. Leibovici, Z. Petrescu and S.A. Ghelberg. 1974. The effecis of long-term administration of organochlorine pesticides (lindane, DDT) on the white rat. Rev. Med. Chir. 78(4): 831-842. (Rom.) (Taken from PESTAB/75/2506)

Petrasek, A.C., I.J. Kugelman, B.M. Austern, T.A. Pressley, L.A. Winslow and R.H. Wise. 1983. Fate of toxic organic compounds in wastewater treatment plants. J. Water Pollut. Control Fed. 55(10): 1286-1296.

Pickering, Q.H. 1983. Chronic toxicity to fathead minnow Pimephales promelas of wastewater from a conventional wastewater treatment system receiving oganic priority pollutants. Environ. Pollut. Ser. A. 31(2): 105-117.

Pimental, D. 1971. Ecological effects of pesticides on non-target species. U.S. EPA, Washington, DC. NTIS PB-269-605.

Podrebarac, D.S. 1984. Pesticide, metal and other chemical residues in adult total diet samples (XIV). October 1977-September 1978. J. Assoc. Off. Anal. Chem. 67: 176-185.

Poradovsky, K., L. Rosival and A. Mesazarosova. 1977. Transpacental permeation of pesticides during normal pregnancy. Cesk. Gynekol. 42: 405-410. (Cited in U.S. EPA, 1980a, 1985a)

Portig, J.P., et al. 1973. Biodegradation of α-hexachlorocyclohexane. I. Glutathione-dependent conversion to a hydrophilic metabolite by rat liver cytosol. Naunyn-Schmied's Arch. Pharmacol. 279: 185. (Cited in U.S. EPA, 1980a)

Probst, G.S., R.E. McMahon, L.E. Hill, C.Z. Thompson, J.K. Epp and S.B. Neal. 1981. Chemically-induced unscheduled DNA synthesis in primary rat hepatocyte cultures: A comparison with bacterial mutagenicity using 218 compounds. Environ. Mutagen. 3(1): 11-32.

Purchase, I.F.H., E. Longstaff, J. Ashby, et al. 1978. An evaluation of sex short-term tests for detecting organic chemical carcinogenesis. Br. J. Cancer. 37: 873-903.

Ramamoorthy, S. 1985. Competition of fate processes in the bioconcentration of lindane. Bull. Environ. Contam. Toxicol. 34: 349-358.

Randall, W.F., W.H. Dennis and M.C. Warner. 1979. Acute toxicity of dechlorinated DDT, chlordane and lindane to bluegill (Lepomis macrochirus) and Daphnia magna. Bull. Environ. Contam. Toxicol. 21(6): 849-854.

Rao, P.S.C. and J.M. Davidson. 1982. Retention and transformation of selected pesticides and phosphorus in soil-water systems: A critical review. ORD, U.S. EPA, Athen, GA. EPA-600/3-82-060.

Rao, P.S.B. and V.K. Venugopalan. 1984.. Lindane induced respiratory changes in juveniles of estuarine fish Mugil cephalus (Linn). Indian J. Mar. Sci. 13(4): 196-198. (CA 102:144468g)

Rao-Kovvali, S.S., S. Ghosh and A.V. Jayanthi. 1980. Chlorinated pesticide residues on flue-cured tobaccos grown in Andra Pradesh. Tobacco Res. 6: 49-56.

Research and Consulting Co., Ltd. 1983. Lindane: Subchronic oral dosing (rat) study. EPA Pesticide Accession No. 250340. (Cited in U.S. EPA, 1985a)

Reuber, M.D. 1979. Carcinogenicity of lindane. Environ. Res. 19: 460-481.

Rickard, D.G. and D.E.R. Dulley. 1983. The levels of some heavy metals and chlorinated hydrocarbons in fish from the tidal Thames. Environ. Pollut. (Ser. B). 5: 101-119.

Rivett, K.F., H. Chesterman, D.N. Kellett, A.J. Newman and A.N. Worden. 1978. Effects of feeding lindane to dogs for periods of up to 2 years. Toxicology. 9(3): 273-289.

Rocchi, P., P. Perocco, W. Alberghini, A. Fini and G. Prodi. 1980. Effect of pesticides on scheduled and unscheduled DNA synthesis of rat lymphocytes and human lymphocytes. Arch. Toxicol. 45(2): 101-108.

Rodgers, J.H., Jr., K.L. Dickson and M.J. Detoer. 1983. Bioconcentration of lindane and naphthalene in bluegills (*Lepomis macrochirus*). *In*: 6th Symp. Aquatic Toxicology and Hazard Assessment, Am. Soc. Test. Mater., Philadelphia, PA. p. 300-311. ASTM STP 802.

Rohrborn, G. 1977. Statement on the potential mutagenicity of lindane. Hooker Rebuttal submission. OPTS, U.S. EPA, Washington, DC. (Cited in U.S. EPA, 1985a)

Sackmauerova, M., O. Palusova and A. Szokolay. 1977. Contribution to the study of drinking water, Danube water and biocenose contamination with chlorinated insecticides. Water Res. 11(7): 551-556.

Saleh, F.Y., K.L. Dickson and J.H. Rodgers, Jr. 1982. Fate of lindane in the aquatic environment: Rate constants of physical and chemical processes. Environ. Toxicol. Chem. 1: 289-297.

Sanders, H.O. 1969. Toxicity of pesticides to the crustacean *Gammarus lacustris*. Bureau of Sport Fish. Wildl. Tech. Paper No. 25. Government Printing Office, Washington, DC. (Cited in U.S. EPA, 1972, 1980b; Pimental, 1971)

Sanders, H.O. 1970. Pesticide toxicities to tadpoles of the western chorus from, *Pseudacris triseriata*, and Fowler's toad, *Bufo woodhousii fowleri*. Copeia. 2: 246-251.

Sanders, H.O. 1972. Toxicity of some insecticides to four species of malacostracan crustaceans. Bur. Sport Fish. Wildl. Tech. Paper 66. (Cited in U.S. EPA, 1972, 1980b)

Sanders, H.O. and O.B. Cope. 1966. Toxicities of several pesticides to two species of *Cladocerans*. Trans. Am. Fish. Soc. 95(2): 165-169.

Sanders, H.O. and O.B. Cope. 1968. The relative toxicity of several pesticides to three species of stoneflies. Limnol. Oceanogr. 13: 112-117.

Sandhu, S.S., W.J. Warren and P. Nelson. 1978. Pesticidal residue in rural potable water. J. Am. Water Works Assoc. 70: 41-45.

Santolucito, J.A. 1975. The use of quantitative EEG for detecting low-level prolonged exposure to pesticides. In: Proc. Int. Symp. Recent Adv. Assess. Health Eff. Environ. Pollut. 4: 2387-2394.

Sax, K. and H.J. Sax. 1968. Possible mutagenic hazards of some food additives, beverages and insecticides. Japan J. Genet. 43: 89-94.

Saxena, M.C., M.A. Siddiqui, A.K. Bhargava, T.D. Seth, C.R. Krishnamurti and D. Kutty. 1980. Role of chlorinated hydrocarbon pesticide in abortions and premature labour. Toxicology. 17: 323-331. (Cited in U.S. EPA, 1985a)

Saxena, M.C., M.K.J. Siddiqui, A.K. Bhargava, C.R. Krishna Murti and D. Kutty. 1981. Placental transfer of pesticides in humans. Arch. Toxicol. 48: 127-134. (Cited in U.S. EPA, 1985a)

Schimmel, S.C., J.M. Patrick, Jr. and J. Forester. 1977. Toxicity and bioconcentration of BHC and lindane in selected estuarine animals. Arch. Environ. Contam. Toxicol. 6(2-3): 355-363.

Schmitt, C.J., J.L. Zajicek and M.A. Ribick. 1985. National pesticide monitoring program: Residues of organochlorine chemicals in freshwater fish, 1980-1981. Arch. Environ. Contam. Toxicol. 14: 225-268.

Schulte-Hermann, R. and W. Parzefall. 1981. Failure to discriminate initiation from promotion of liver tumors in a long-term study with the phenobarbital-type induced α-BHC and the role of sustained stimulation of hepatic growth and monooxygenases. Cancer Res. 41(1): 4140-4146.

Schwarzenbach, R.P. and J. Westall. 1981. Transport of nonpolar organic compounds from surface water to groundwater, laboratory studies. Environ. Sci. Technol. 15: 1360-1367.

Sethunathan, N. and T. Yoshida. 1973. Degradation of chlorinated hydrocarbons by Clostridium sp. isolated from lindane-amended, flooded soil. Plant Soil. 38: 663-666.

Seuge, J. and R. Bluzat. 1979. Chronic toxicity of carbaryl and lindane to the freshwater mollusc Lymnea stagnalis L. Water Res. 13(3): 285-293. (Fre.)

Seuge, J. and R. Bluzat. 1983. Chronic toxicity of three insecticides (carbaryl, fenthion and lindane) in the freshwater snail Lymnaea stagnalis. Hydrobiologia. 106(1): 65-72.

Shahin, M.M. and R.C. Von Borstel. 1977. Mutagenic and lethal effects of α-benzene hexachloride, dibutyl phthalate and trichloroethylene in Saccharomyces cerevisiae. Mutat. Res. 48(2): 173-180.

Sharma, A.K. and S. Gosh. 1969. A comparative study on the effects of certain chemical agents on chromosomes. Acta Biol. Acad. Sci. Hung. 20: 11-21. (Cited in IARC, 1979)

Sharom, M.S., J.R.W. Miles, C.R. Harris and F.L. McEwen. 1980. Persistence of 12 insecticides in water. Water Res. 14(8): 1089-1093.

Shell Oil Co. 1982. The effects of water hardness, temperature and size of test organisms on the susceptibility of freshwater shrimp *Gammarus pulex* (L.) to toxicants. Office of Toxic Substances, U.S. EPA, Washington, DC. TSCA 8d submission 878210074.

Shimazu, H., N. Shiraishi, T. Akematsu, N. Ueda and T. Sugiyama. 1976. Carcinogenicity screening tests on induction of chromosomal aberrations in rat bone marrow cells *in vivo*. Mutat. Res. 38: 347.

Shirasu, Y., M. Moriya, K. Kato, A. Furuhashi, and T. Kada. 1976. Mutagenicity screening of pesticides in the microbial system. Mutat. Res. 40: 19-30. (Cited in U.S. EPA, 1985a)

Shivanandappa, T. and M.K. Krishnakumari. 1981. Histochemical and biochemical changes in rats fed dietary benzene hexachloride. Indian J. Exp. Biol. 19(12): 1163-1168.

Shivanandappa, T. and M.K. Krishnakumari. 1983. BHC-induced testicular dysfunction in rats. Acta Pharmacol. Toxicol. 51(1): 12-17.

Shivanandappa, T., M.K. Krishnakumari and S.K. Majumder. 1982. Inhibition of steroidogenic activity in the adrenal cortex of rats fed benzene hexa chloride BHC. Experientia (Basel). 38(10): 1251-1253.

Shtenberg, A.I. and C. Mametkuliev. 1976. Effect of the γ-isomer of hexachlorocyclohexane (HCCH) on the functional state of the sexual glands in rats. Vopr. Pitan. 4: 62-67. (Rus.) [CA 85(17):117679z]

Shukla, G.S. and Omkar. 1983. Acute toxicity of insecticides to a freshwater prawn Macrobrachium lamarrei (M. Edwards). Indian J. Environ. Health. 25(1): 61-63. [CA 100(3):18986u]

Siddiqui, M.K.J., M.C. Saxena and C.R. Krishna Murti. 1981a. Storage of DDT and BHC in adipose tissue of Indian males. Int. J. Environ. Anal. Chem. 10: 197-204. (Cited in U.S. EPA, 1985a)

Siddiqui, M.K.J., M.C. Saxena, A.K. Bhargava, C.R.K. Murti and D. Kutty. 1981b. Chlorinated hydrocarbon pesticides in blood of newborn babies in India. Pestic. Monit. J. 15(2): 77-79.

Singh, D.N., R.K. Tyagi and R.S. Panwar. 1981. Toxicity of some organic biocides to a freshwater fish, Cyprinus carpio communis. J. Environ. Biol. 2(3): 41-46. [CA 97(9):67466c] (Cited in Pickering, 1983)

Slooff, W. 1979. Detection limits of a biological monitoring system based on fish respiration. Bull. Environ. Contam. Toxicol. 23(4-5): 517-523.

Snow, J.R. 1958. A preliminary report on the comparative testing of some of the newer herbicides. In: Proc. 11th Ann. Conf. Southeast Assoc. Game Fish Comm. p. 125-132. (Cited in U.S. EPA, 1971, 1972)

Srivastava, P.N. and A.S. Narain. 1982. Leukocytic and hemostatic reactions of the Indian catfish, Heteropneustes fossilis, subjected to environmental pollution by sewage, fertilizers and insecticides. Acta Pharmacol. Toxicol. 50(1): 13-21.

Stanley, C.W., J.E. Barney, II, M.R. Helton and A.R. Yobs. 1971. Measurement of atmospheric levels of pesticides. Environ. Sci. Technol. 5: 430-435.

Steffey, K.L., J. Mack, C.W. MacMonegle and H.B. Petty. 1984. A ten-year study of chlorinated hydrocarbon insecticide residues in bovine milk in Illinois, 1972-1981. J. Environ. Sci. Health B. 19: 49-65.

Stein, K., J. Portig, H. Fuhrmann, M. Koransky and G. Noack. 1980. Steric factors in the pharmacokinetics of lindane and α-BHC in rats. Xenobiotica. 10(1): 67-78.

Stephenson, R.R. 1983. Effects of water hardness, water temperature and size of the test organisms on the susceptibility of the freshwater shrimp, Gammarus pulex (L.) to toxicants. Bull. Environ. Contam. Toxicol. 31: 459-466.

Stewart, D.K.R. and M.D. Chisholm. 1971. Long-term persistence of BHC, DDT and chlordane in a sandy loam soil. Can. J. Soil Sci. 61: 379-383.

Strachan, W.M.J. 1985. Organic substances in the rainfall of Lake Superior: 1983. Environ. Toxicol. Chem. 4: 677-683.

Strachan, W.M.J. and H. Huneault. 1979. Polychlorinated biphenyls and organochlorine pesticides in Great Lakes precipitation. J. Great Lakes Res. 5: 61-68.

Strand, J.A., III, B.E. Vaughan and J.T. Cummins. 1967. Pesticidal Control of Contaminant Macro-Invertebrates Encountered in Laboratory Culture of Marine Sea Weeds. NTIS AD-648854.

Streit, B. 1979. Uptake, accumulation and release of organic pesticides by benthic invertebrates. 3. Distribution of ^{14}C-atrazine and ^{14}C-lindane in an experimental 3-step food chain microcosm. Arch. Hydrobiol. 55: 373-400.

Sugihara, S., K. Hirao, M. Hananouchi and N. Ito. 1975. Ultra-structural studies on hepatomas induced by benzene hexachloride (BCH). J. Electron Microsc. 24: 192.

Sugiura, K., T. Washino, M. Hattori, E. Sato and M. Goto. 1979. Accumulation of organochlorine compounds in fishes. Differences of accumulation factors by fishes. Chemosphere. 8(6): 359-364.

Sullivan, J.H. 1980. Pesticide residues in imported species. A survey for chlorinated hydrocarbons. J. Agric. Food Chem. 28(5): 1031-1034.

Szymczynski, G.A. and S.M. Waliszewski. 1981a. Comparison of the content of chlorinated pesticide residues in human semen, testicles and fat tissues. Andrologia. 13(3): 250-252. (Cited in U.S. EPA, 1985a)

Szymczynski, G.A. and S.M. Waliszewski. 1981b. Content of chlorinated pesticides in human semen of a random population. Int. J. Andrology. 4(6): 674-699. (Cited in U.S. EPA, 1985a)

Takeda, T. 1978. Effects of DDT, BHC and PCB on the growth of fish. Kyushu Daigaku Nogakubu Gakugei Zasshi. 32(4): 141-145. (Jap.) [CA 91(5):33793t]

Tanabe, S., T. Mori and R. Tatsukawa. 1983. Global pollution of marine mammals by PCBs, DDTs and HCHs (BHCs). Chemosphere. 12: 1269-1275.

Tanabe, S., H. Tanaka and R. Tatsukawa. 1984. Polychlorobiphenyls, Σ DDT and hexachlorocyclohexane isomers in the western North Pacific ecosystem. Arch. Environ. Contam. Toxicol. 13(6): 731-738.

Tanaka, K., N. Kurihara and M. Nakajima. 1979. Oxidative metabolism of lindane and its isomers with microsomes from rat liver and house fly abdomen. Pestic. Biochem. Physiol. 10(1): 96-103. (Cited in U.S. EPA, 1980a, 1985a)

Tarzwell, C.M. 1959. The toxicity of some organic insecticides to fishes. *In*: Proc. 12th Ann. Conf. Southeast Assoc. Game Fish Comm. p. 233-239. (Cited in U.S. EPA, 1971)

Thorpe, E. and A.I.T. Walker. 1973. Toxicology of dieldrin (HEOD). II. Comparative long-term oral toxicity studies in mice with dieldrin, DDT, phenobarbitone, β-HCH and γ-BHC. Food Cosmet. Toxicol. 11(3): 433-442.

Tooby, T.E. and F.J. Durbin. 1975. Lindane residue accumulation and elimination in rainbow trout (*Salmo gairdnerii*) and roach (*Rutilus rutilus*). Environ. Pollut. 8(2): 79-89.

Tooby, T.E., P.A. Hursey and J.S. Alabaster. 1975. Acute toxicity of 102 pesticides and miscellaneous substances to fish. Chem. Ind. (London). 12: 523-526.

Tsui, P.T.P. and P.J. McCart. 1981. Chlorinated hydrocarbon residues and heavy metals in several fish species from the Cold Lake area in Alberta, Canada. Int. J. Environ. Anal. Chem. 10: 277.

Tu, C.M. 1976. Utilization and degradation of lindane by soil microorganisms. Arch. Microbiol. 108: 259-263.

Turner, J.C. and V. Shanks. 1980. Absorption of some organochlorine compounds by the rat small intestine -- in vivo. Bull. Environ. Contam. Toxicol. 24(5): 652-655.

Tzoneva-Maneva, M.T., F. Kaloianova and V. Georgieva. 1971. Influence of diazinon and lindane on the mitotic activity and the caryotype of human lymphocytes, cultivated in vitro. In: Proc. XII Internat. Cong. Soc. Blood Transfusions, Moscow, 1969, Bibl. Haemat. No. 38, part 1, Basel Karger. p. 344-347. (Cited in IARC, 1979)

U.S. EPA. 1972. Water Quality Criteria 1972. A report of the committee in water quality criteria. Washington, DC. NTIS PB-236-199.

U.S. EPA. 1973. Unpublished report. BHC-lindane. Criteria and Evaluation Division, Office of Pesticide Programs, Washington, DC. 280 p. (Cited in U.S. EPA, 1985a)

U.S. EPA. 1976. Quality Criteria for Water. Washington, DC. EPA 440/9-76-023. NTIS PB-263-943.

U.S. EPA. 1977. Computer print-out of non-confidential production data from TSCA Inventory. Office of Pesticides and Toxic Substances, CID, Washington, DC.

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Hexachlorocyclohexane. Criteria and Standards Division, Washington DC. NTIS PB 297-924/3.

U.S. EPA. 1980b. Ambient Water Quality Criteria Document for Hexachlorocyclohexane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Water Regulations and Standards, Washington, DC. EPA 440/5-80-054. NTIS PB 81-117657.

U.S. EPA. 1981. Treatability Manual Vol. 1. Treatability data. Office of Research and Development, Washington, DC.

U.S. EPA. 1982a. Health Effects Assessment for B-Hexachlorocyclohexane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. TR-82-524.

U.S. EPA. 1982b. Health and Environmental Effects Profile for Lindane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC. TR-82-664.

U.S. EPA. 1984a. Health Effects Assessment for Lindane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC. NTIS PB86-134673/AS.

U.S. EPA. 1984b. Summary Table of Hazard Ranking for Reportable Quantities under CERCLA. OHEA-C-073.

U.S. EPA. 1985a. Drinking Water Criteria Document for Lindane. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. (Final draft)

U.S. EPA. 1985b. Reference Values for Risk Assessment. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste, Washington, DC.

U.S. EPA. 1986a. Integrated Risk Information System (IRIS). Reference Dose (RfD) for Oral Exposure for Lindane. Online (Verification date 01/22/86). Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH.

U.S. EPA. 1986b. Guidelines for Carcinogen Risk Assessment. Federal Register. 51(185): 33992-34003.

Veith, G.D., D.L. DeFoe and B.V. Bergstedt. 1979. Measuring and estimating the bioconcentration factor of chemicals in fish. J. Fish. Res. Board Can. 36(9): 1040-1048.

Velson, F.P.J. and D.F. Alderdice. 1967. Toxicities of two insecticides to young coho salmon. J. Fish. Res. Board Can. 24: 1173-1175.

Vonk, J.W. and J.K. Quirijns. 1979. Anaerobic formation of alpha-hexachlorocyclohexane from gamma-hexachlorocyclohexane in soil and by Escherichia coli. Pestic. Biochem. Physiol. 12(1): 68-74.

Wassermann, M., M. Ron, B. Bercovici, D. Wassermann, S. Cucos and A. Pines. 1982. Premature delivery and organochlorine compounds: Polychlorinated biphenyls and some organochlorine insecticides. Environ. Res. 28(1): 106-112.

Weisse, I. and M. Herbst. 1977. Carcinogenicity study of lindane in the mouse. Toxicology. 7: 233-238.

Welch, R.M. and J.W.A. Findlay. 1981. Excretion of drugs in human breast milk. Drug Metab. Rev. 12(2): 261-278.

Wellborn, T.L.J. 1971. Toxicity of some compounds to striped bass fingerlings. Prog. Fish-Culturist. 33(1): 32-36.

Whitten, D.K. and C.J. Goodnight. 1966. Toxicity of some common insecticides to tubificids. J. Water Pollut. Control Fed. 38: 227-235.

WHO (World Heath Organization). 1967. 1966 Evaluations of some pesticide residues in food. WHO/Food Add./67/32. p. 126-147. (Cited in IARC, 1979)

WHO (World Heath Organization). 1969. 1968 Evaluations of some pesticide residues in food. WHO/Food Add./69.35. p. 17-31. (Cited in IARC, 1979)

Williams, D.T., E.R. Nestmann, G.L. Lebe, F.M. Bevoit and R. Olson. 1982. Determination of mutagenic potential and organic contaminants of Great Lakes drinking water. Chemosphere. 11: 263-276.

Wilson, A.J. 1965. Chemical assays. In: Ann. Rep. Bureau of Comm. Fish. Biolog. Lab., Gulfbreeze, FL. U.S. Bur. Comm. Fish. Circ. 247. (Cited in Pimental, 1971)

Windholz, M., Ed. 1983. Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ. p. 789.

Yamamoto, T., T. Egashira, Y. Yamanaka, T. Yoshida and Y. Kuroiwa. 1983. Initial metabolism of gamma-hexachlorocyclohexane (γ-HCH) by rat liver microsomes. J. Pharmacobio-Dyn. 6(10): 721-728.

Yamato, Y., M. Koyanaga and T. Watanabe. 1983. Comparative bioaccumulation and elimination of BHC isomers in short-necked clam Venerupis japonica and guppy Poecilia reticulata. Bull. Environ. Contam. Toxicol. 31(3): 352-359.

Zaroogian, G.E., J.F. Heltsch and M. Johnson. 1985. Estimation of bioconcentration in marine species using structure-activity models. Environ. Toxicol. Chem. 4(1): 3-12.

Zesch, A., K. Nitzsche and M. Lange. 1982. Demonstration of the percutaneous resorption of a lipophilic pesticide and its possible storage in the human body. Arch. Dermatol. Res. 273: 43-49. (Cited in U.S. EPA, 1985a)

Zoeteman, B.C.J., K. Harmsen, J.B.H.J. Linders, C.F.H. Morra and W. Sloof. 1980. Persistent organic pollutants in river water and groundwater on the Netherlands. Chemosphere. 9: 231-249.

APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2B. John Wiley and Sons, NY. p. 2879-3816.

Clayton, G.D. and F.E. Clayton, Ed. 1982. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2C. John Wiley and Sons, NY. p. 3817-5112.

Grayson, M. and D. Eckroth, Ed. 1978-1983. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Volumes.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., Littleton, MA. 575 p.

IARC (International Agency for Research on Cancer). IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans. WHO, IARC, Lyons, France.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

NTP (National Toxicology Program). 1986. Toxicology Research and Testing Program. Chemicals on Standard Protocol. Management Status.

Ouellette, R.P. and J.A. King. 1977. Chemical Week Pesticide Register. McGraw-Hill Book Co., NY.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Co., NY.

SRI (Stanford Research Institute). 1984. Directory of Chemical Producers. Menlo Park, CA.

U.S. EPA. 1985. Status Report on Rebuttable Presumption Against Registration (RPAR) or Special Review Process. Registration Standards and the Data Call in Programs. Office of Pesticide Programs, Washington, DC.

U.S. EPA. 1985. CSB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422, Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.